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ENERO 1985



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Columna del Editor

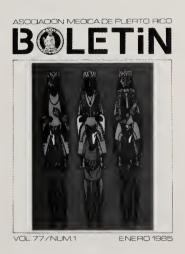


on este primer número del 1985 se comienza el cuarto año consecutivo de este servidor como Presidente de la Junta Editora de nuestro Boletín, el cual tiene la distinción de ser la publicación médica de mayor duración de todas las fundadas en América en el siglo 20. Al analizar este dato nos llena de satisfacción el saber que se ha sido parte activa en la historia de la medicina de nuestro país. Esto a su vez permite que se haga otro esfuerzo para poder continuar nuestra tarea editorial, que por los standards implican más autoimpuestos. Trabajo, sacrificios y sin sabores para el año que acaba de comenzar. Se hará la labor con el mismo interés, dedicación y ahinco que el primer día pero debe entenderse que con la publicación del último número de este volumen 77 queda cumplida nuestra encomienda.

El 1985 nos trae un nuevo Secretario de Salud en la persona del doctor Luis Izquierdo Mora. La Asociación Médica de Puerto Rico siente gran satisfacción en que uno de sus colaboradores más eficaces y distinguido Ex-Presidente haya sido seleccionado para tan prestigioso e importante puesto en el gobierno del país. La Junta Editora del Boletín de la Asociación Médica de Puerto Rico felicita al doctor Izquierdo Mora y una vez más pone a su disposición nuestro órgano oficial para todo aquello que sea relevante para nuestra clase médica y beneficioso para la salud del pueblo de Puerto Rico.

Milanimii Ino

Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico



NUESTRA PORTADA

Los Tres Reyes Magos. Serigrafía del artista puertorriqueño Eduardo Vera Cortés. El autor nació en Utuado, en 1926. En 1949, entra en el taller de gráfica de la Comisión de Parques y Recreos de Puerto Rico, donde aprende el arte de la serigrafía con el maestro Félix Bonilla Norat. Recibe clases de Julio Rosado del Valle y de Irene Delano. Aprende a hacer carteles en el taller de la División de Educación de la Comunidad y cursa estudios de escultura y modelaje con el maestro español Francisco Vázquez Díaz "Compostela", en el Instituto de Cultura Puertorriqueña. En 1960, recibe una beca del Departamento de Instrucción Pública para estudiar en la Escuela Nacional de las Artes del Libro en México, así como en la Escuela La Esmeralda y en el Centro Superior de Artes Aplicadas. Ha recibido premios en el Ateneo Puertorriqueño (talla en madera) (1953), en el Festival del Café, en Ponce (pintura) (1954) y Premio Internacional de la Alcoa Steamship Company, por su pintura Vida de Perros (1955).

Ha exhibido su obra en el Riverside Museum, de Nueva York (1957); Primera Bienal de México (1958); Museo de la Universidad, Museo de Ponce, Ateneo Puertorriqueño, Galería Colibrí, Galería Campeche, Galería Pintadera, Instituto de Cultura, y otras salas de Filadelfia, Boston, Roma, La Habana y Kingston. En 1975, ganó una mención de honor en el Festival de Navidad, del Ateneo, en ocasión de su Centenario.

La obra en nuestra portada está inspirada en las imágenes de madera de los Reyes Magos que tanto gustan tallar nuestros artesanos. En esta serigrafía Vera-Cortés le imparte una forma más moderna y de claro corte impresionista a las tres figuras cuyo día se celebra este mes por la comunidad latina mundial.

ESTUDIOS CLINICOS

Liver Preservation

Luis H. Toledo-Pereyra, MD, PhD

Abstract: Sharing of harvested hepatic allografts, between distant center, is currently limited by the length of successful hypothermic storage using currently available storage solutions and techniques. TP-II, a hyperosmolar colloid solution, was compared with Collins (C-2) solution for 24-hour hypothermic storage prior to transplantation. between distant centers, is currently limited by the length of animals receiving TP-II preserved livers (n=6) ($X \pm SD$, 12.6 \pm 15.8 days) as compared to the survival of animals transplanted with Collins preserved hepatic allografts (n=6) (X \pm SD, 4.3 \pm 7.2 days). Hepatic allograft survival after 24 hour preservation in TP-II solution was also not significantly different from fresh non-preserved allografts $(15.2 \pm 17.0 \, \text{days})$. These results encourage further work in this area for eventual facilitation and improvement of liver preservation methods for clinical transplantation.

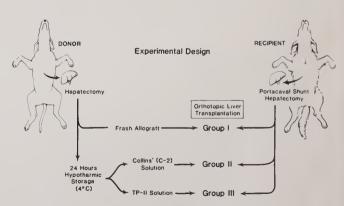
The logistics of hepatic transplantation would be greatly facilitated by the development of improved solutions for hypothermic storage of liver allografts.³ Recent experimental and clinical work by our group has indicated that improved results can be obtained using TP-II, a modified silica gel fraction (SGF) base hyperosmolar solution for hypothermic storage of kidney allografts.¹¹, ¹² The aim of our present series of experiments was to compare the efficacy of this TP-II solution with Collins (C-2) solution, which is currently being used clinically,² for hypothermic storage (24 hours) of canine liver allografts.

Materials and Methods

Unrelated mongrel dogs weighing between 20 and 25 kg were used as donors and recipients for orthotopic liver transplantation using our previously published protocol.¹³ The larger animals were used as liver allograft recipients and the smaller animals were used as donors. Sodium thiamylal was used for induction of anesthesia (1.25 mg/Kg) and maintained with fluothane (0.5-2.0%). Oxygen was administered at a rate of 2-2.5 L/min.

Donor Hepatectomy - Donor animals were anesthetized as previously described. One liter of 5% dextrose in water was administered intravenously during the dissection using standard techniques. Potassium chloride (4 mEq), and isoproterenol hydrochloride (0.4 mg) were also given at this time. Heparin (10,000 U) was also administered 10 minutes prior to vascular cross-clamping. One unit of donor blood was collected in acid citrate dextrose bags for later transfusion into the recipient.

Liver preservation - After removal, livers were immediately placed in a sterile pan containing saline ice. Hepatic allografts to be transplanted into recipients in Group I (n=6) were then flushed through the portal vein and hepatic artery with heparinized Ringer's lactate solution (10,000 U/L) and immediately transplanted. (Figure 1) Liver allografts to be transplanted into animals in Group II (n=6) were flushed with Collins (C-2) solution prior to hypothermic storage in the same solution for 24 hours. Liver allografts of Group III (n=6) recipients were similarly flushed and hypothermically stored for 24 hours (as in Group II) with TP-II solution. Sodium bicarbonate was added to the preservation solution at the level of the portal vein site at 4-8 hours and 16-24 hours before transplantation to adjust the pH to between 7.7-8.0. Prior to transplantation, all hypothermically stored livers were reflushed with heparinized Ringer's lactate solution (200 ml).



Followup for all groups - minimal immunosupprassion (azathioprina 5.0-2.5 mg/kg/day), SMA-12 datarminations, livar bloosy at death or sacrifice

From the Department of Surgery, Sections of Transplantation and Surgical Research, Mount Carmel Mercy Hospital, Detroit, Michigan This work was supported by an institutional grant from the Mount Carmel Research and Education Corporation.

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Figure 1. Experimental design. Liver allografts were removed from donor animals and either transplanted as fresh allografts or hypothermically stored for 24 hours in Collins (C-2) or TP-II solution.

Preservation Solutions - Collins's solution (C-2) (Travenol base) prepared in the research laboratories was used for preservation of livers in Group II. TP-II solution was prepared in the hospital pharmacy for use on the liver allografts in Group III. Table I compares the composition of the two solutions.

Recipient Operation - Recipient animals underwent a hepatectomy as previously described.¹³ A portacaval shunt was created after the recipient liver and major vessels were entirely dissected out. An external bypass was also constructed between the left external iliac and left external jugular veins.² Adequate blood flow was maintained through the bypass by a nonpulsatile pump (Sarns). The bypass was initially primed with 250 ml Ringer's lactate. Heparin (2,000 U) was administered 10 minutes before opening the portacaval shunt and the bypass. In addition, one unit (500 ml) of donor blood that had been previously collected during harvesting was given to the liver allograft recipient prior to opening the external bypass to avoid hypotension. Orthotopic liver transplantation was then performed using standard techniques.¹³ Sodium bicarbonate (NaHCO₃, 8.92 m Eq in 10 ml), methylprednisolone sodium succinate (Solumedrol, 500 mg intravenously), and isoproterenol hydrochloride (at a maximum dose of 0.4 mg by slow intravenous drip) were administered to each recipient prior to revascularization of the liver.

Recipient Follow-up and Immunosuppression - Recipient animals were given intravenous fluid support with 5% dextrose in water (500-1500 ml) for the first few days after transplantation until the oral route was established. Daily SMA-12 determinations were performed for the first week, biweekly for 2 weeks, and periodically thereafter, including serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and lactic acid dehydrogenase (LDH) levels were made to assess

TABLE I Comparison of Collins' (C-2) and TP-II Solutions for Hypothermic Storage of Liver Allografts

The state of the s		
	C-2	TP-II
рН	7.0	7.2*
Na + (mEq/L)	10	130
K + (mEg/L)	115	65
Ca ++ (mEq/L)		8.0
$PO_4 - (mEq/L)$	115	50
C1 - (mEq/L)	15	64*
$HCO_3 - (mEq/L)$	10	8.0
Mg ++ (mEq/L)	30	1.5
Osmolarity (mOsm/L)	320	520
$SO_4 - (mEq/L)$	60	
Glucose (gm/L)	25	40
Total Protein (gm/L)		5.8
Albumin (gm/L)		4.3
Total Triglycerides (mg/L)		25
IgG (mg/dl)		510
IgA (mg/dl)		205
IgM (mg/dl)		78

Chloride is the only change seen in TP-II when compared with previous preparations.11, 12 The pH measured practically the same at 7.2.

liver function. Minimal immunosuppression was given to all recipients (azathioprine, 5.0 mg/Kg/day for 3 days, followed by 2.5 mg/Kg/days until death of sacrifice). Biopsies were taken of the hepatic allografts for light microscopy at the time of sacrifice or post mortem examination.

Statistical Analysis - Student t-test and chi-square analysis were used to compare the immediate and longterm survival of the liver allografts.

RESULTS

Table II displays the comparative mean survival and the functional results immediately after transplantation for the three study groups. In addition, Figure 2 details the survival of each of the individual animals in the groups. All fresh nonpreserved liver allografts in Group I survived > 72 hours after transplantation. Recipients of liver allografts (Group III), which had been hypothermically stored for 24 hours in TP-II solution, demonstrated somewhat similar long-term survival as the nonpreserved freshly transplanted controls (Group I). Four of six liver recipients in Group III survived > 24 and > 72 hours after surgery. However, the survival of recipients of livers preserved for 24 hours with Collins' (C-2) solution was severely compromised and only two of six recipients in Group II, preserved with Collins' solution, survived > 24 hours and one of these animals survived > 72 hours after engraftment.

TABLE II distand Long Term Function of Liver Allografts After Orthotonic Liver Transplantation

			Surv	ival*	Mean Survival Days	Survival
Group	N	Preservation	>24 hours	>72 hours	(X + SD)**	Range
1	6	None-fresh	6/6	6/6	15.2 ± 17.0	4, 6, 6, 7, 20, 48
11	6	24 hr. HS, Collins' (C-2)	2/6	1/6	4.3 ± 7.2	I, 1, 1, I, 3, 19
Ш	6	24 hr. HS,	4/6	4/6	12.6 ± 15.8	I, 1, 6, 7, 19, 42

 $(>72 \, hrs.) \, p>.10$ Statistical analysis (T-test)- Group 1 vs. Group II,p<.10, Group 1 vs. Group III, p>.25, Group II vs. Group III, p>.10

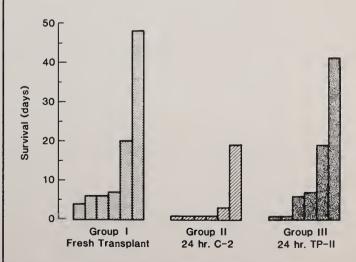


Figure 2. Individual survival of animals in each experimental group. Hypothermic storage of livers with TP-II solution yielded improved survival over the Collins (C-2) preserved group.

HS- Hypothermic storage

• - Statistical analysis Chi-square)- Group II vs. Group III (>24 hrs) p>.25, Group II vs. Group III

Recipients in the non-preserved control group and well preserved liver allografts in Group III, using TP-II, showed a minimal increase in LDH and SGOT after transplantation. The serum bilirubin and alkaline phosphatase demonstrated an insignificant increase. Those animals surviving more than 72 hours after grafting had a practically normal liver function profile. However, most of the dogs that were preserved with Collins solution and one dog that was preserved in TP-II showed the most significant functional alterations, including highly abnormal LDH and SGOT levels and a moderate initial increase in serum bilirubin and alkaline phosphatase levels. All animals demonstrated an increase in all liver functional values prior to death.

Table III shows the cause of death of all transplanted animals. Bleeding and vascular thrombosis were more frequently seen in the Collins stored group, however, examples were also noted in the other groups. Rejection was seen only in long-term survivors.

Histological findings correlated well with functional results. Postmortem biopsies of livers in Group I demonstrated minimal physiological damage. Hepatic histology of livers preserved for 24 hours with Collin's solution indicated preservation damage which was evidenced by hepatocyte disruption, severe swelling, and frequent changes compatible with hemorrhagic necrosis. Whereas, liver specimens from allografts in Group III

TABLE III

Cause of Death Foi	iowing Orthot	opic Liver Tra	nsplantation
Cause of Death	Group I	Group II	Group III
Bleeding	1	2	1
Peritonitis	1	1	1
Vascular thrombosis	1	2	1
Pneumonia	1	0	0
Rejection	2	1	2
Undetermined	0	0	1
Total	6	6	6

recipient that had been hypothermically stored for 24 hours with TP-II solution showed minimal to moderate physiological damage identified by some cellular swelling, but not exhibiting irreversible changes.

DISCUSSION

Experimental efforts directed toward extending periods of hepatic hypothermic storage have been limited by the liver's extreme sensitivity to hypoxia. Preservation studies in the past decade and a half have utilized both crystalloid and colloid solutions for liver preservation^{1,4-10} (Table IV). For short periods of storage, adequate induction of hypothermia appears to be more important

TABLE IV

	Se	elective Review of Experimen	tai Liver Hypothem	ic Storage
Author	Year	Hypothermic Storage Solution	Tlme	Results
Schalm, et al ¹³	1969	Plasma-bicarbonate glucose-procaine	3-31 ₂ hours	No differences in function or survival between fresh and hypothermically stored livers.
Splig, et al ⁸	1971	Plasma-dextrose	6-8 hours	Porcine livers successfully stored 6 to 8 hours.
Mieny and Myburgh ⁴	1971	Dextran-electrolyte- sorbitol	4-24 hours	Extended survival in 3 or 4 after 4-7 hours HS, 2 of r after 19-20 hours, and 0 of 3 after 24 hours.
Otte, et al6	1973	Ringer's, Collins (C-2), or C-2 + isoproterenol	up to 19 hours	Successful HS up to 19 hours with C-2 + isoproterenol
Toledo-Pereyra and Najarian ⁹	1974	Ringer's + heparin + procaine, Dextran 40 + heparin + procaine, or Sack's (20 min. warm ischemia to all trans- planted livers)	3 hours	Only livers preserved for 3 hours with Sack's survived for prolonged periods.
Benichou, et al ¹	1977	Ringer's plasma, Collins	9, 18 hours	All three solutions equal for 9 hours HS, Collins slightly superior after 18 hours.
Toledo-Pereyra, et al ¹⁰	1979	Ringer's, Sack's, or MSGF	24 hours	Successful 24 hours preservation using Sack's and MSGF. Slightly better with MSGF.
Monden and Fortner ⁵	1982	Ringer's M-solution, M-solution + PGI2	24, 48 hours	2 of 5 dogs survived greater than with M-solution, 6 to 6 survived greater tan 48 hours with M-solution + PGI2

than the type of solution utilized since Ringer's lactate, modified plasma and Collins' solutions worked equally well for up to 9 hours. 11 However, for 18 hours of preservation as expected the Collin's solution yielded better results than the Ringer's lactate solution. Subsequent studies in our laboratories¹⁰ have demonstrated better preservation of livers even for 24 hours in either hyperosmolar colloid (modified silica gel fraction) or crystalloid (Sack's) solutions, even though better results were seen with the colloid solutions. Twenty four hours preservation with Ringer's solution, however, significantly damaged the liver allografts. Recent work by Monden and Fortner⁵ has indicated the potential beneficial effects of utilizing a modified Sack's solution together with prostaglandin I for 24 and 48 hour hypothermic storage of canine livers.

Our most recent work in preservation has improved the previous hyperosmolar silica gel base solution for hypothermic storage by adding dextrose and potassium phosphate. Preliminary tests on canine kidney allografts showed that TP-II was superior to Euro'-Collins solution for 48 to 72 hours of hypothermic storage. 11 In the first clinical trial, the immediate and long-term post-transplantation ourcomes of TP-II stored kidneys were comparable to those of contralaterally harvested donor kidneys preserved by hypothermic pulsatile perfusion methods. These promising results led us to the application of TP-II to liver preservation by hypothermic storage. The findings of our current study indicate that TP-II appears to be an acceptable solution for 24 hour periods of hypothermic storage of nonischemic canine liver allografts. Collins' (C-2) solution, however, does not appear to provide similar protection to liver allografts during hypothermic storage for 24 hours. Although all of the factors contributing to the differences in efficacy between the two solutions have not been elucidated, the high osmolarity of the colloid TP-II solution with high concentrations of phosphate, glucose, and potassium probably contributed to improved liver preservation.

These results should encourage further experimental work to improve liver preservation using hypothermic storage techniques. We realize that TP-II could be further improved to achieve consistent preservation for periods of 24 hours, since 2 of 6 animals in the TP-II preserved group did not survive beyond 24 hours. In addition, it is essential that stringent criteria be established for the performance of preservation solutions used on organs, such as the liver, whose function cannot be replaced by artificial means. Hopefully, in the future, clinical programs will be able to utilize these methods to facilitate the logistics of organ retrieval and sharing between distant institutions.

Resumen: La Preservación y el transporte de hígados humanos ha sido limitada por la pobre tolerancia de estos órganos a la isquemia caliente y fría que normalmente reciben después de la disección y extirpación. En este trabajo estudiamos dos soluciones, la TP-II (una solución coloide hiperosmolar) y la solución de Coliins (una solución cristaloide intracelular) en la preservación de hígados de perro por 24 horas. La solución TP-II resultó mejor que la

solución Collins, en que la primera mantuvo los animales vivos por 12.6±15.8 días después del transplante de hígado; en cambio la solución Collins mantuvo vivos los animales por 4.4±7.2 días. Estos resultados parecen mostrar que soluciones coloides hiperosmolares son mejores que soluciones cristaloides, y es posible que en esta forma podamos obtener períodos más largos de preservación hepática.

Acknowledgement

The technical assistance of Gerald MacKenzie and the participation of Debra A. Gordon in the elaboration and editing of this work are greatly appreciated.

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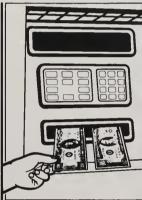
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What can you do for hypertensives like Mary B?

Uncontrolled

Moderate hypertension (160/110 mmHg) with recent increases despite medication.

Forgetful

Misses appointments and frequently fails to follow instructions.

Overweight

At 73 largely sedentary... weight even more of a problem now.

Coexistent diabetes

On daily insulin after diet, exercise, and oral agents failed.

Patient description is a hypothetical composite based on clinical experience and evaluation of data

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Mary B represents 2,165 women over 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians!

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Mary B's difficult age group?

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Use in diabetes

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta-blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.³⁻⁶

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁷ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy!



For Mary B...and virtually all your hypertensive patients

TENORMIN® (atendal)





For Mary B... and virtually all your hypertensive patients

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN\(^1\) (atenolol), a synthetic, beta_1-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide.
4-[2'-hydroxy-3'-[1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266 ft its a relatively polar hydrophilic compound with a water solubility of 26 5 mg/ml at 37\(^2\) C and a log partition coefficient (octanol/water) of 0.23 ft is freely soluble in 1N HCl (300 mg/ml at 25\(^2\)C) indicated in chloroform (3 mg/ml at 25\(^2\)C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Sion. It may be used alone or concominarity with other aritinypernessive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenoloi slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overfangina pectoris, when discontinuation of TENORMIN is planned, the patients should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if with-drawal symptoms occur.

should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta;-stimulating agent (bronchodillator) made available. If dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic

the last dose and anesthesa if Irearment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (e.g. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (e.g. protound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients it a beta-blocking agent is required. Beta blockers may mask fachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

rould be monitored closely

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce verigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinopenesis. Mutagenesis. Impairment of Fertility: Two long-term (maximum dosing dura-

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various endangenic bridge review the the review of the formal formal

recommended numan dose, do not initiate a carcinogenic potential in rodenis nesulis of various mutagenicity studies support this finding. Fertility of male or temale rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenoiol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuulation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenoiol (starting at 15 mg/kg/day or 7.5 times the maximum recommended

human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not see
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human will. Since

potential risk to the retus

**Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

arenoid
Pediatric Use: Salety and effectiveness in children have not been established
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates
were derived from controlled studies in which adverse reactions were either volunteered by the
patient (U.S. studies) or elicited (eg. by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when
these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo
is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

from the U.S. Studies (volunted as the terror and elected side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCUL AR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL. diarrhea (2%-0.%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0.0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), light-headeness (3%-0.7%), tredness (26%-13%), latigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL. diarrhea (3%-2%), nausea (3%-1%)
GASTROINTESTINAL. diarrhea (3%-2%), nausea (3%-1%)
MISCELLANEOUS. There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored tollowing cessation of therapy.

tored following cessation of therapy POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress. Central Nervous System: Reversible mental depression progressing to catationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time an place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic collits

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practiol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practoic reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart tailure, hypotension

bronchospasm, and hypoglycemia In the case of overdosage, treatment with TENORMIN should be stopped and the patient care-tully observed TENORMIN can be removed from the general circulation by hemodialysis. In addi-tion to gastric lavage, the following therapeutic measures are suggested it warranted:

Brandcardia: Atropine or another anticholinergic drug

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker

Congestive Heart Failure: Conventional therapy

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or noe

epinephrine may be useful in addition to atropine and digitalis

Bronchospasm: Antinophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to

one to two weeks if an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day increasing the dosage beyond 100 mg a day is unlikely to produce any turther benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance talls below 35 ml/min/173 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Atenolol Creatinine Clearance (ml min/1 73 m²) Flimination Halt-life (hrs) Maximum Dosag 16-27 >27 50 mg daily 15-35 50 mg every other d

Patients on hemodiallysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked talls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat light and most sturk. Store unit-dose and calendar packages at controlled room.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled roo

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Role of Electrophysiologic Testing in the Selection of Patients Requiring Pacemaker Implantation

Héctor García, M.D.* José R. Martínez, M.D.* Juan M. Aranda, M.D., F.A.C.C.**

Peurologic symptoms such as light headedness, dizziness or syncope are frequently reported in patients with conduction abnormalities or recurrent cardiac arrhythmias. Non invasive testing such as 24 hour ambulatory electrocardiographic recording and treadmill exercise tests are very helpful in making a definite diagnosis and assessing the results of therapy, either antiarrhythmic agents or permanent electrical pacing. When non invasive testing as well as extensive neurologic examination fails to reveal a definite cause for the patients's symptoms, electrophysiologic evaluation of the cardiac conduction system may be of clinical value.

Evaluation of Sinus Node Function

The sick sinus syndrome may manifest itself as sinus bradycardia, sinus arrest and/or sino-atrial exit block, often with intermittent atrial tachyarrhythmias.¹⁻² The diagnosis of sick sinus syndrome may be suspected on the basis of the clinical symptoms and the electrocardiographic findings. Bedside maneauvers, 24 hours electrocardiographic monitoring and on occasions, electrophysiologic testing is required before making a definite diagnosis.

Measurement of the sinus node recovery time (SNRT) is performed by pacing the right atrium for 30 to 180 seconds at rates 10 beats/minute above the control value.³⁻⁴ The pacing rate is then increased at 10 beat increments to rates of 140 to 150 per minute. The SNRT is measured from the last paced beat to the first sinus beat. Since the peak recovery time may vary with the atrial,

pacing rate, it is recommended that determination of sinus node recovery time be measured following multiple pacing rates from just above the sinus rate to at least 140 beats per minute.

In 43 normal subjects, Mandel et al reported values of 1041±56 msec as compared to 4372±67 msec in patients with sick sinus syndrome.⁵ The corrected sinus node recovery time is calculated by substracting the baseline sinus cycle length from the post pacing recovery time. Values less than 525 msec have been reported as normal.⁶

Occasionally, one may find abnormal sinus node recovery times at slower pacing rates when atrial-sinus conduction is 1:1 and normal sinus node recovery times at faster pacing rates. The explanation for this paradox is that at faster rates not all of the paced atrial beats are able to penetrate and depolarize the SA node because of SA nodal entrance block. The physiologic response after the administration of atropine is a shortening of the sinus node recovery time. On occasions, a paradoxical response is found. It has been stated that in these paradoxical responses, atropine abolishes the SA entrance block and allows penetration of atrial paced beats into the sinus node. This results in increased sinus suppression and prolongation of the SNRT.⁷

Besides measuring SNRT, corrected SNRT and the administration of atropine, evaluation of subsequent post pacing cycles may contribute to the diagnosis of sick sinus syndrome. If prolongation of cycle lengths after the first post pacing cycle is a multiple of the prepacing cycle length, it may indicate sinus node exit block, a manifestation of SSS. These secondary pauses increase the usefulness of atrial pacing in the evaluation of patients with sick sinus syndrome.⁸⁻¹²

Effect of Atropine on Sinus Node Function

In therapeutic doses (1-2 mg IV), a tropine increases the rate of the sinus node and enhances A-V nodal conduction. It has been published that in normal subjects it increases the heart rate to over 90 beats/minute¹² and

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shortens the sinus node recovery time. Mandel⁵ and Strauss¹¹ found an increase in heart rate of 20 to 23% (52-64 beats/min.) in 51 patients with proven or suspected sick sinus syndrome.

It seems that the administration of atropine is an adequate screening test for a patient suspected of having sick sinus syndrome. A normal response to atropine does not rule out the diagnosis.

Diagnostic Value of Atrial Pacing

- 1. Sinus node recovery time
- 2. Corrected sinus node recovery time before and after atropine
- 3. Identification of Secondary Pauses
- 4. Sino-atrial Conduction Time

Clinical Value of Corrected SNRT

In a series of 103 elderly patients with sinus brady-cardia, Gann⁸ et al, found that symptomatic patients with an abnormal corrected SNRT, who received permanent pacemakers, were free of symptoms when followed for 4 years.

All patients with sinus bradycardia, syncope, and abnormal corrected SNRT had their symptoms controlled after pacemaker therapy. An abnormal corrected SNRT predicted therapeutic success after pacemaker implantation in 91% of his patients with dizziness.⁸

Autonomic Dysfunction or Intrinsic Sinus Node Dysfunction

The autonomic nervous system influences the automaticity of the SA node. Jordan⁹ et al have reported a method of separating extrinsic (autonomic dysfunction) from intrinsic sinus node dysfunction. Blockade of the autonomic system is achieved by the administration of .04 mg/Kg of atropine and 0.2 mg/Kg of propranolol. The sinus rate obtained after autonomic blockade is termed the intrinsic heart rate. In a group of 17 patients, after the administration of atropine and propranolol, 10 patients were found to have normal intrinsic heart rates and 7 had abnormal intrinsic heart rates. The former group had normal corrected SART, while the latter had prolonged corrected SART. These 2 groups could not be differentiated by their corrected SART before atropine and propranolol were administered. The clinical value of Jordan's study is that the patients with normal intrinsic sinus node function may benefit more from medical therapy.

The Sino-Atrial Conduction Time

The sino-atrial conduction time (SACT) is the time that it takes an impulse to enter the sinus node from the peri sinus node tissue. Patients with symptomatic sinus bradycardia appear to have a SACT longer than those with asymptomatic sinus bradycardia.¹⁰

During spontaneous sinus rhythm (Al), premature atrial stimulation (A2) is performed with progressive shortening of the coupling interval (A1-A2). The following intervals are then measured:

A1-A1 = spontaneous cycle length

A1-A2 = the coupling interval of the premature atrial stimulation

A2-A3 = the interval between the premature atrial stimuli and the spontaneous sinus beat following the premature stimulation

The following responses may be found:

1.
$$AI-AI = AI-A2 + A2-A3/2$$
 or $2 \times (AI-AI) = AI-A3$

This indicates that the premature atrial depolarization did not depolarize or reset the sinus node. It did not interfere with the automaticity of the SA node, however, it interfered with conductivity of the sinus impulse to the atrium.

2. 2x (Al-A1) > Al-A3

This indicates that the premature atrial depolarization enters and resets the sinus node.

3. AI-AI = AI-A3

This indicates that the atrial premature beat has been interpolated. It did not interfere with the automaticity of the SA node or the conductivity of the sinus impulse.

4. A1-A1 < A1-A3

This indicates that the atrial premature beat entered and was reflected back to the atrial tissue (sinus node reentry).

Initially Strauss¹¹ assumed that antegrade and retrograde conduction between the site of stimulation in the atrium to the sinus node were equal. He proposed that when less than compensatory pauses were detected; 2x(A1-A1) > A1-A3 it indicated conduction from the atrium to the sinus node (which is reset) and back. Therefore, sino atrial conduction was given by the following formula: (A2-A3)-(A1-A1) divided by 2. Recently they proposed that the SACT was more reliably calculated as (A2-A3)-(A1-A1). Normal values 125 - 240 msec.

In 1977, Narula and his group proposed a simplified method to calculate the SACT. Atrial pacing is performed for 8 beats at a rate greater than or equal to 10 beats/minute over the spontaneous sinus rate. He assumed that this brief mode of pacing will not cause overdrive suppression of the sinus node or affect its automaticity, but will reset the SA node. The pause following the last paced beat minus the spontaneous cycle length will reflect the SACT. The correlation between the two methods is adequate.

Electrophysiological Indicators for Pacemaker Therapy in Patients with Sick Sinus Syndrome

The most important aspects of the evaluation of patients with suspected sick sinus syndrome are an adequate history, physical examination and 12 lead electrocardiographic tracing. If the patients is asymptomatic, close clinical follow up and patient education are advised. If the patient is symptomatic, the aim of the clinical evaluation is to corroborate that his symptoms are secondary to the sinus node disorder. An office or bedside evaluation should include 24 hour Holter recording, exercise test and atropine test. If these non-invasive procedures show evidence of SA block and SA arrest, particularly if associated with symptoms, permanent pacing is indicated and non-invasive tests are not required.

Evaluation of A-V Node Function

Neurological symptoms such as dizziness, light headedness and syncope may also be secondary to dysfunction of the A-V node. Overall mortality in patients with A-V node dysfunction is low¹³ and permanent pacing is reserved for those patients that are symptomatic and whose symptoms are secondary to A-V node dysfunction. A-V node dysfunction may be the only electrophysiologic abnormality detected in patients with unexplained syncope.¹⁴

Evaluation of A-V node function should be performed before and after the administration of atropine since vagal tone may have a significant influence on the function of the A-V node. A-V Wenckeback has been reported in normal students and athletes secondary to vagal effect.

The determination of A-V nodal conduction time (AH interval) before and during atrial pacing provides a direct measurement of A-V nodal function (normal value 50-120 msec). Prolongation of the A-H interval during incremental pacing is a physiologic effect. Second degree A-V nodal block should occur at pacing rates over 130/minute. Its appearance at rates below 130/minute indicates A-V node dysfunction. The Absolute and relative refractory periods determination is another parameter used to evaluate A-V nodal function. Its determination has been made possible with the atrial extrastimuli technique. The pacing site appears to influence the A-H conduction pattern and determination of refractory periods.

This is particularly true in patients with short PR intervals. ¹⁶ The rate at which A-V Wenckeback occurs is higher and the refractory periods are shorter when atrial pacing is performed in the left atrium than the right atrium. ¹⁶

There are two particular clinical settings in which determination of A-V nodal conduction is very valuable in selecting a particular mode of therapy:

A. Concealed His bundle extra systole: Extra systoles originating in the His bundle are usually manifested in the surface electrocardiogram as premature beats arising from the A-V junction with or without ventricular aberration. At times, these premature His bundle depolarization, as a result of exit block, become concealed. Its presence may be suspected due to several electrocardiographic abnormalities that result from retrograde depolarization of the A-V node; sudden PR prolongation, alternation of the PR interval, premature non conducted atrial beats and A-V block. Electrophysiologic evaluation may be indicated when concealed His bundle extrasystoles induce a type II second degree A-V block. Symptomatic type II second degree A-V block due to concealed His bundle extrasystoles is treated with anti-arrhythmic agents not with pacemaker therapy.

B. Type I second degree A-V block: This type of A-V conduction delay occurring with a normal QRS complex is almost always due to block in the A-V node. In this situation seldom is a pacemaker required. At times, type I second degree A-V block

with normal QRS complex results from conduction delay within the His bundle itself. This form of block may be seen in elderly females (although it has also been reported in males), and behaves quite different from conduction delays in the A-V node. It frequently progresses to higher degree of intra His bundle block requiring a permanent electrical mode of therapy. In this clinical setting, evaluation of the conduction system helps in the clinical management of the patients involved.

Evaluation of His bundle function: The His bundle electrogram is a trifascicular deflection inscribed before the right ventricular electrogram obtained through a tripolar catheter placed across the tricuspid valve. The deflection itself measures less than 25 msec.¹⁷ It has been published that conduction delays within the His bundle are manifested either by His bundle deflections that measure over 25 msec or by split (H-H1) His bundle depolarizations. In the electrophysiologic evaluation of patients with conduction delays in the A-V junction, it is imperative to look for the "split" His bundle depolarization, this is particularly true in those patients with marked prolongation of the AH interval and normal HV intervals specially if they are elderly with neurological symptoms. In this situation, the proximal His bundle deflection is absent.

The same applies to those patients with marked HV prolongation and normal QRS complexes. If the distal (H¹) deflection is not inscribed, the conduction delay will be localized distal to the His bundle instead of the His bundle itself.

Evaluation of Infra His Conduction: Scherlag et al described the technique to record the HV interval.¹⁸ It indicates conduction time between the bundle of His and the ventricular myocardium. Its value has been reported between 35 to 55 msec. Values over 55 msec indicate conduction delays in the His bundle, bundle branches or Purkinje system.

During atrial pacing, the H-V should remain constant at any given rate. Pacing induced block below the His bundle is always abnormal and indicates advanced conduction disease. It is an indication for permanent electrical pacing in a symptomatic patient with bundle branch block in the surface electrocardiogram.¹⁹ There are several clinical settings in which electrophysiological evaluation of the infra His conduction system is of great clinical value.

A. In acute myocardial infarction: The appearance of bundle branch block, specially right bundle branch block, and left anterior hemiblock in patients with acute anterior wall infarction, indicates a relatively high risk of sudden cardiac death in the year following the infarction. Those patients that develop transient complete AV block or Type II AV block, permanent electrical pacing is indicated²⁰ without the need for electrophysiologic study. It is present controversial wheather those patients with right bundle branch block without left anterior hemiblock, who do not develop transient high grade A-V block during the acute infarction,

need electrophysiologic evaluation. However, Lie et al²¹ demonstrated that a prolongued H-Vinterval in survivors of an acute infarction who developed new bifascicular block, indicate an increased risk for future development of AV block and sudden death. Electrophysiologic evaluation is recommended for this group of patients to select those that appear to benefit with permanent electrical pacing.

B. In chronic bundle branch block and neurologic symptoms (bundle branch block not associated with acute infarction): In the most comprehensive study published, Scheiman et al²² performed electrophysiologic studies in 313 patients with chronic (not associated with acute infarction) bundle branch block. The patients were followed up for 3 years. Group I (97 pts.) had H-V interval < 55 msec. Group II had H-V intervals of 55 to 69 msec (99 pts), and group III was characterized by H-V intervals ≥ 70 msec (117 pts). The groups were comparable except for a higher incidence of heart disease in Group III patients. Group III had a higher incidence of high degree AV block (12%) than group I and II (4% and 2% respectively). As suggested in other studies, 23-25 the longer the H-V interval, the greater the incidence of high grade A-V block; (of 17 pts with H-V intervals ≥100 msec, 4 (24%) developed complete AV block). Sixty two patients underwent permanent prophylactic pacemaker insertion. On follow-up, mortality and sudden death were similar between those with permanent pacemaker as compared to those without pacemaker, however, symptom relief was significantly more common among patients with permanent pacers. From these and other studies, it appears that patients with neurologic symptoms, bundle branch block and prolonged H-V intervals, in whom no other cause for the neurologic symptomatology is present, will benefit from permanent pacing. The data appears to suggest that those with bundle branch block, H-V intervals greater than 100 msec or block distal to the His bundle during atrial pacing are at a high risk for developing spontaneous high grade A-V block. It is possible that prophylactic permanent pacemaker may be of benefit in the latter situation.

Programmed Stimulation in the Evaluation of Patients with Conduction Disorders

A complete electrophysiologic evaluation of patients with neurological symptoms such as dizziness, light headedness and syncope is not complete without use of programmed atrial and ventricular stimulation. This can be accomplished during spontaneous sinus rhythm or during atrial and ventricular paced rhythms. Neurological symptoms in patients with or without pre-existing bundle branch can be secondary to reentrant supraventricular or ventricular tachycardia. These tachyarrhythmias can be induced with the use of single or double extrastimuli. If provoked, anti arrhythmic therapy is then guided to suppress electrical induction of the tachycardia.

Modalities of Permanent Electrical Pacing

Permanent demand ventricular inhibited pacemaker (VVI) has been the method of choice of sustain adequate heart rates in patients with A-V block or bradyarrhythmias. Some patients with this mode of pacing have experienced symptoms such as fatigue, dizziness or syncope even when the pacemaker system is working well. In others, decompensation of heart failure and pulmonary congestion appeared after ventricular pacing was started. The term pacemaker syndrome was used to describe the symptoms related to the hemodynamic effects of ventricular pacing.

Mechanism

When atrial and ventricular contractions are not sequential as in VVI pacing, the ventricle is deprived of the atrial contribution to ventricular filling. As a result of this, the mean atrial pressure increases, left ventricular end diastolic pressure decreases and there is a fall in cardiac output. Symptoms of dizziness, hypotension and fatigue may appear.

Although the lack of atrial transport appear to be an important factor in the development of the syndrome, other hemodynamic effects have been associated with ventricular pacing. Retrograde VA conduction can occur during ventricular pacing resulting in reciprocal beating. In a series of patients who underwent electrophysiologic studies, retrograde conduction was present in 39% of patients with heart block and 90% of patients with sick sinus syndrome²⁶ and normal AV conduction. The retrograde atrial activation will cause regular repetitive a trial contractions within the ventricular ejection period. The atria contracting against closed AV valves will result in systemic and pulmonary venous regurgitation and pulmonary congestion. This could explain in part the congestive heart failure observed after ventricular pacing in patients who were otherwise compensated before ventricular pacing.

Another consequence of intact retrograde VA conduction is that ventricular pacing may produce regular echo beats following each paced beat. Since these reciprocal beats occur close to the ventricular systole, they are not hemodynamically effective, and activate the sensing mechanism of the demand pacemaker delaying the next ventricular paced beat. The result of this is a bradycardialike situation.

Adequately timed atrial systole is also important in the mechanism of mitral valve closure. Mitral regurgitation can occur when the ventricle contracts without a preceeding atrial systole. Atrial systole induces an increase in ventricular pressure and a ventricular atrial pressure gradient which effectively closes the mitral valve.

During ventricular pacing, if A-V dissociation or heart block is present, P waves occurring in early diastole (prolonged PR interval >200 msec) will prematurely close the mitral valve and result in a decrease filling of the left ventricle, decrease stroke volume and cardiac output. The earlier the P wave occurs in diastole, the shorter the ventricular filling period. If the P wave occurs with the onset of diastole, closure and reopening of the mitral

valve occurs. Replacement of the ventricular pacemaker with a more physiologic unit is the treatment of choice of the pacemaker syndrome.

The improved hemodynamic response to dual chamber pacing (DDD, DVI) has been recognized. In patients with poorly compliant ventricle such as patients with rheumatic heart disease, calcific aortic stenosis, hypertensives and coronary artery disease, the atrial contribution to cardiac output is important. When deciding whether dual chamber pacing will be of value, blood pressure monitoring and cardiac output determination are of value during spontaneous rhythm, VVI and dual chamber pacing. During VDD, DDD or VAT pacing the atrial sensing electrode cannot distinguish between antegrade or retrograde atrial conduction. A ventricular depolarization that is conducted to the atrium is sensed by the atrial lead and triggers a ventricular response. If this is sustained, a pacemaker mediated tachycardia is generated. For a pacemaker tachycardia to occur, the retrograde VA impulse must fall outside the refractory period of the atrial pacemaker. The electrophysiologic study before or at the time of permanent pacemaker implantation provide a mechanism to study retrograde conduction. The ventricles are incrementally paced to the upper rate limit of the pacemaker (usually 150 beats/ minute). If retrograde conduction is present and falls outside the atrial lead refractory period, the patient is prone to develop pacemaker induced rhythm disturbances. To avoid this, the atrial refractory period is lengthened or the upper late limit of the pacemaker is decreased. By re-programming the pacemaker system to a non atrial sensed mode (DVI), the pacemaker induced tachycardia could also be avoided. As pacing technique becomes more sophisticated, the electrophysiological evaluation of the patients with rhythm disturbances will be an indispensable step to decide on the most useful modality of pacing.

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La Enteritis por Campylobacter fetus

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Resumen: El Campylobacter jejuni ha sido reconocido recientemente como un patógeno importante en los humanos, y si se utilizan los medios de cultivo apropiados, probablemente se recobra de pacientes con diarreas agudas con la misma frecuencia que se recobran Salmonella o Shigella. Este organismo es responsable no sólo de cuadros de enteritis y diarreas agudas, sino que ha sido asociado a eritema nodoso, endocarditis, meningitis, abortos y proctitis entre otras enfermedades.

Usualmente, el curso es autolimitado, recuperándose el paciente en menos de una semana. Sin embargo, en aquellos pacientes con diarreas prolongadas o cuadros de enteritis recurrentes, se recomienda tratamiento con eritromicina por vía oral. Los medios de cultivos simplificados y prácticos nos permiten hacer el diagnóstico de enteritis por campylobacter, por lo que debemos considerar este organismo y ordenarlo en las muestras de rutina en el paciente que se presenta con diarreas agudas.

El Campylobacter fetus ha sido reconocido como un patógeno en animales e implicado en casos de aborto en el ganado y en las ovejas. En el 1947 se reconocen infecciones en el humano causadas por este organismo y se asocia a múltiples enfermedades sistémicas en el paciente inmunocomprometido o debilitado.¹ Pero adquiere importancia clínica cuando se logra aislar de las heces fecales de pacientes con enteritis aguda.²

Microbiología y Laboratorio

El Campylobacter jejuni es una bacteria gram-negativa, mótil, curva, delgada, y pequeña. Posee un flagelo polar y su movimiento en forma de dardo es rápido y se produce al girar sobre su eje mayor. La pared celular, cuyo lipopolisacárido posee propiedades endotóxicas, es típica de los organismos gram-negativos. El campylobacter es microaerofilico y no fermentativo. Originalmente fue clasificado bajo el género vibrio (Vibrio fetus), pero Sebald, Véron y Chatelain demuestran que existen diferencias marcadas entre las características bioquímicas, requerimientos nutricionales y composición de los ácidos nucléicos entre ambos géneros, y proponen separarlos ya en el 1973.4

Programa de Enfermedades Infecciosas y Departamentos de Investigación y Medicina, Centro Médico de la Administración de Veteranos y Escuela de Medicina de la Universidad de Puerto Rico 00936

Solicitar reimpresos a: Julie Rodríguez, M.D., Programa de Enfermedades Infecciosas (151), Centro Médico de la Administración de Veteranos, GPO, Box 4867, San Juan, Puerto Rico 00936 El género campylobacter se divide en dos grupos de acuerdo a su habilidad de producir catalasa. Los catalasa negativo, *C. sputorum* y *C. bubulus*, no se reconocen como patógenos para el hombre, mientras que el *C. fetus*, que es catalasa positivo, sí se ha asociado con enfermedad en el ser humano (*C. fetus ss jejuni, ss intestinalis*) (Tabla I).⁵

TABLA I

Designación Actual	Enfermedad en Animales	Enfermedad en Humanos	Enfermedad Subyacente
C. fetus subsp. yeyuni	Abortos en ovejas	Enteritis Meningitis Artritis	
C. fetus subsp. intestinalis	Abortos en ovejas y cabras	Endocarditis Meningitis	Cirrosis Enfermedades cardiovasculares
		Artritis séptica Tromboflebitis Pulmonía	Malignidad Alcoholismo Preñez (?)
		Abscesos del pulmón Abortos	
		Natimuertos Prematuros	
		Sepsis neonatal	

Tomado de Torphy D. E. et al (5)

En el 1971, Cooper y Slee⁶ reportan el primer medio selectivo para aislar el *Campylobacter*, ya que no puede ser aislado utilizando los medios usuales de coprocultura. En el 1972, Dekeyser lo aisla de las heces fecales de pacientes utilizando unos filtros especiales² y para el 1973, Butzler⁷ y el 1977 Skirrow,⁸ reportan una incidencia de 5 y 7.1% respectivamente de cultivos positivos para *Campylobacter* en pacientes evaluados por gastroenteritis aguda; sin embargo, no logran aislarlo en personas asintomáticas. Existen actualmente métodos prácticos para cultivar este organismo de las heces fecales de los pacientes. Las muestras de excreta deben inocularse en medios selectivos: Skirrow's, ⁸ Butzler's ⁹ o Campy-BAP.³

Existen varias clasificaciones para este organismo (Tabla II). La Dra. Elizabeth King en el 1962¹⁰ llama vibrios relacionados ("related vibrios") a lo que en el manual de Bergey se clasifica como *Campylobacter fetus ss fetus*. Los autores europeos utilizan frecuentemente la clasificación de la doctora King, mientras que en los Estados Unidos se utiliza la clasificación del manual de Bergey.

TABLA II

Manual de Bergey		nimo Taxo de acuerdo King		Ecologia	F nfermedad	Caracteristica de Crecimiento
Campylobacter fetus ss. fetus	C fetus ss. venerealis	Vibno	V fetus ss vene- realis	No es flora normal, Se encuentra en semen de ganado, fluido del prepucio, moco cervical	Abortos y esterilidad en cabras Transmisión venerea en animales	
				No crece en tracto G I de bumanos o animales	No está asociada a enfermedad en humanos	
	C fetus ss venerealis biotipo intermedio					
C fetus ss. intestinalis	C fetus ss. fetus	Vibrio fetus	V fetus ss. intes- tinalis	No es flora normal, Se puede encontrar en placentas y conte- nido gástrico de fettos de ganado abortados, en la bilis, en tractos G U. y G I	Aborto en ovejas Aborto en cabras Causa usual de enfermeda sistémica en humanos	Crece a 25°C No crece a 42°C
				Puede crecer en el tracto G.I. de humanos		

Presentación Clínica

Al igual que con otros patógenos intestinales, las infecciones por *C. jejuni* no siempre están acompañadas por síntomas. Existen excretores asintomáticos y casos leves entre los contactos de los pacientes. Por otro lado, también se han reportado casos de colitis recurrentes que simulan el cuadro de colitis ulcerativa o enfermedad de Crohn.¹¹, ¹² También se han reportado muertes; pero como es de esperarse, esto ha ocurrido en pacientes debilitados o inmunosuprimidos.

El período de incubación es aproximadamente de tres a cinco días, pero puede variar desde uno hasta diez días.¹³, ⁸, ¹⁴ El cuadro clínico es diferente en el adulto, por lo que lo discutiremos por separado.

El 66% de los pacientes adultos presentan un pródromo de fiebre alta (40°C), malestar general, mialgias y dolor de espalda.8, 9, 13 Este pródromo dura aproximádamente 24 horas y es seguido de náusea, vómitos y dolor abdominal que se localiza en el área periumbilical inicialmente y luego puede ser referido a las fosas iliacas. Al día siguiente¹⁵ comienza el cuadro de diarreas que se caracterizan por ser acuosas, mal olientes, y en algunos casos por estar acompañada de sangre.8, 15 Las diarreas duran de 3 a 5 días, pero el dolor abdominal por lo general dura por más tiempo, es precipitado por la ingestión de alimentos y mejora con la evacuación. La mayoría de los pacientes se recuperan en menos de una semana, pero hasta un 20% de los pacientes pueden tener recaídas o presentar una enfermedad severa en la cual persiste la fiebre y las diarreas sanguinolentas.

Los niños tienden a presentar una enfermedad menos severa y el cuadro clínico varía con la edad del paciente. El 90% de los niños presentan sangre en la excreta entre el segundo y cuarto día de la enfermedad. Karmali¹⁶ encuentra que todos los niños mayores de tres meses de edad presentan fiebre alta (40.5°C), mientras que los niños menores de tres meses permanecían afrebriles. La fiebre, si presente, desaparece al cuarto día. La frecuencia de las evacuaciones va a variar desde unas pocas hasta veinte diarias, pero no hubo reporte alguno de deshidratación en estos pacientes. 9, 16 Hay que considerar, sin

embargo, que Karmali llevó a cabo el estudio en Toronto donde el clima es templado y quizás en el trópico la deshidratación puede ocurrir. Tan sólo el 60% de los niños refirieron dolor abdominal, pero si consideramos sólo los niños mayores de dos años, la frecuencia de esta queja aumenta hasta un 95%. El 30% de los niños en este estudio presentaron vómitos. Otros autores reportan estadísticas similares. El contaje de blancos varía desde normal hasta marcadamente elevado y la velocidad de sedimentación globular generalmente es de 70mm/hr o más. 13

Es usual encontrar títulos serológicos de 1:40 y si se usan los sueros pareados, se nota un aumento de títulos de cuatro veces el inicial. En personas saludables, los títulos están comunmente bajos.¹⁸

Complicaciones

Además de la enteritis y de la colitis con cultivos positivos, que es el cuadro clínico más comúnmente asociado a Campylobacter, existen una variedad de otros síndromes asociados a este organismo. Se ha visto asociado a la enteritis, un cuadro de abdomen agudo. En niños y adultos jóvenes se ha descrito adenitis y apendicitis debido a la edema y a la congestion de la pared intestinal;⁸, ¹³ la mayoría de las veces la cirugía se podría evitar si se piensa en el diagnóstico y se hace un extendido de las heces buscando el campylobacter.

Otras condiciones que se han asociado a la enteritis por *Campylobacter* es la artritis.^{19, 20} En uno de estos reportes, Berden¹⁹ describe un paciente de 20 años con artritis reactiva luego de enteritis por *Campylobacter*. Es importante notar que este paciente poseía el antígeno de histocompatibilidad HLA-B27. Urman describe el curso clínico de un paciente con el diagnóstico del síndrome de Reiter²⁰ donde las exacerbaciones de su enfermedad estaban asociadas a diarreas y en dos ocasiones se le aisla *C. fetus* en la sangre. Nunca se logra aislar el foco de infección. Otras enfermedades asociadas a este organismo son eritema nodoso, pústulas de piel, endocarditis, pericarditis, meningitis, peritonitis, abortos, proctitis en el homosexual y otros.^{18, 9, 14}

Patología

Si nos dejamos llevar por la presentación clínica de diarreas agudas y acuosas nos inclinaríamos a pensar que la principal patología se encuentra en el intestino delgado (yeyuno e ileo) y varios reportes de pacientes sometidos a cirugía^{9, 10} confirman este hecho. Existen, además, dos reportes post-mortem de yeyunitis hemorrágica en un adulto y en una niña de cinco meses.^{9, 21, 22} La adenitis mesentérica también se ha asociado a este organismos.^{5,23}

Sin embargo, los cambios patológicos no se limitan al área del intestino delgado, ya que estudios recientes realizados por Lambert, ¹¹ Willoughby, ²¹ Price²² y Blaser ¹² demuestran envolvimiento del colon. Este hallazgo se sospechaba porque consistentemente estos pacientes tienen episodios de sangrado rectal, asociado con leucocitos en las heces. A pesar de estos reportes de patología, los reportes de sigmoidoscopía son negativos ^{11, 21, 22, 12} aunque los estudios de las biopsias varían en la interpretación.

De los nueve pacientes estudiados por Price, a 8 se les hizo biopsias;²² de éstos, a 3 se les reportó mucosa normal, mientras que a 5 se les encontró cambios de una proctitis no específica. Los hallazgos histológicos demostraron colecciones aisladas de polimorfonucleares, abscesos aislados, achatamiento de las criptas y edema marcado entre las criptas y la muscularis mucosa. Estos cambios histológicos de proctitis infecciosas aunque característicos, no son específicos de ningún organismo en particular. Además, existe un solapamiento histológico entre estos hallazgos y las enfermedades inflamatorias del intestino.²²

Willoughby,²¹ aunque tan sólo reporta un caso, éste tiene seguimiento histológico durante la fase aguda y la fase convalesciente. En la fase aguda él encontró un infiltrado mayormente de polimorfonucleares, aunque otros autores han reportado la infiltración de células mononucleares, neutrófilos y eosinófilos, resultando en abscesos de las criptas y en ulceraciones de la mucosa.¹⁴

Patogenesis

Existen tres mecanismos patogenéticos básicos según lo discutido por Buztler y Skirrow⁹ que explican el desarrollo de las diarreas infecciosas en general: a) producción de enterotoxinas, b) invasión local y c) la fiebre entérica. En este último tipo de infección los organismos invaden la mucosa y pueden invadir la sangre.

Buztler y Skirrow encuentran que el 16% de las cepas de campylobacter que ellos estudiaron eran capaces de producir una enterotoxina termoestable. Además, existen datos que demuestran la capacidad invasiva de este organismo.9

Epidemiología

Reservorio y modo de transmisión. Las aves y los mamíferos son el principal reservorio para el campylobacter. El C. jejuni ha sido recobrado de las heces fecales de pollos, pavos y otras aves salvajes. Este organismo puede ser un comensal en el intestino de los cerdos, ganado, ovejas, caballos, cabras, roedores y monos. Los perros y gatos son los animales domésticos más frecuentemente infectados con campylobacter.³, ²⁴, ²⁵

C. jejuni ha sido recobrado, además, en aguas frescas y agua salada, 26 y se ha demostrado que el organismo sobrevive en aguas frescas hasta cinco semanas. 27 Las heces fecales de animales y personas infectadas pueden contener organismos viables hasta 4 semanas y representar la fuente de infección del ambiente. 27 Este organismo también se ha asociado al consumo de leche no pasteurizada. 28, 29

El Campylobacter parece ser la causa más importante de diarreas agudas en todos los países, ya que es el organismo más frecuentemente aislado en pacientes con diarreas agudas. Es el organismo bacteriano más frecuentemente aislado en pacientes con diarreas agudas (Tabla III). Revisando estos estudios podemos concluir que C. jejuni es el organismo responsable de aproximadamente 7.6% de las diarreas agudas y que menos del 1% de la población es un portador asintomático. En la Tabla IV,

se compara la frecuencia con que se aisla el campylobacter de pacientes con diarreas agudas contra otros patógenos comunes.

TABLA III

Autor	Lugar	# de pacientes con diarrea	# y % con cultivos (+) para C. fetus	# de pacientes asintomáticos (control)	# y % de cultivo (+) en el grupo control
Butzler (7)	Bruselas "Worcester"	900	45 (5%)	1,000	13 (1.3%)
Skirrow (8)	Inglaterra Manchester	803	57 (7.1%)	194	0
Dale (33)	Inglaterra Surrey	182	14.(7.6%)	60	1.(1.6%)
Tanner (38)	Inglaterra Edinburgo	330	19 (5.8%)	120	1.(0.8%)
Brunton (32)	Escocia Hartford	196	17 (8.7%)	50	0
Bruce (31)	Inglaterra Kwanda	280	39 (13.9%)	156	1
Del Mol (36)	Africa	204	22 (11.0%)	58	0
Blaser (37)	Denver	532	26 (5.1%)	157	0
Pearson (23)	Southampton	860	36 (4 2%)	?	2 (?%)
	Montreai Canada	1,004	43 (4 3%)	176	0
Promedio			7 6%		0.6%

TABLA IV

Lugar Autor condisers									
Solubampton (23) Parson Solubampton (23) Solubampton (24) Parson Solubampton (25) Parson Solubampton (26) Solubampton (27) Parson Solubampton (28) Parson Soluba	Lugar	Autor	pacientes	con	pacientes	pacientes	con E. coli	# de pacientes con otros organismos	
8 (2.9%) Montreal (17) Pai 1,004 43 (4.3%) 51 (5.1%) 14 (1.4%) — Yersina 28 (2.8%) Denver (37) Blaser 514 26 (5.1%) 19 (3.7%) 13 (2.53%) — G. lambd 4.(7.8%) Edinburgo (32) Brunton 196 17 (8.7%) 5 (2.5%) 19 (9.7%) — G. lambd 13 (6.63%) Southampton (23) Pearson 860 36 (4.2%) 24 (2.8%) 8 (.9%) 6 (0.7%) —	Manchester (33)	Dale	182	14 (7 6%)	1 (.5%)	2 (1.1%0	1 (0.5%)	C. lambdia 5 (2.7%)	
28 (2.8%) Denver (37) Blaser 514 26 (5.1%) 19 (3.7%) 13 (2.53%) - G. lambdd 4 (.78%) Edinburgo (32) Brunton 196 17 (8.7%) 5 (2.5%) 19 (9.7%) - G. lambdd 13 (6.63%) Southampton (23) Pearson 860 36 (4.2%) 24 (2.8%) 8 (.9%) 6 (0.7%)	Hereford (31)	Bruce	280	39 (13 9%)	12 (4 3%)	11 (3.9%)	5 (1.8%)	Parásistos 8 (2.9%)	
4 (.78%) Edinburgo (32) Brunton 196 17 (8.7%) 5 (2.5%) 19 (9.7%) G. lambd 13 (6.63%) Southampton (23) Pearson 860 36 (4.2%) 24 (2.8%) 8 (.9%) 6 (0.7%)	Montreal (17)	Pai	1,004	43 (4 3%)	51 (5.1%)	14 (1.4%)	-	Yersinia 28 (2.8%)	
13 (6.63%) Southampton (23) Pearson 860 36 (4 2%) 24 (2.8%) 8 (.9%) 6 (0.7%)	Denver (37)	Blaser	514	26 (5.1%)	19 (3.7%)	13 (2.53%)	-	G. lambdia 4 (.78%)	
	Edinburgo (32)	Brunton	196	17 (8.7%)	5 (2.5%)	19 (9 7%)		G. lambdia 13 (6.63%)	
Inglaterra (22) Price 29 9 (31 0%) 7 (24 13%) 3 (10.3%)	Southampton (23)	Pearson	860	36 (4 2%)	24 (2.8%)	8 (.9%)	6 (0.7%)		
	Inglaterra (22)	Price	29	9 (31 0%)	7 (24 13%)	3 (10.3%)	-	-	

Edad y Sexo. La información que existe sobre la tasa de infección por campylobacter por edad y sexo es basada mayormente en los datos de cultivos de pacientes con diarrea.⁹

La incidencia por edad depende de cómo se analicen los datos; pero la mayoría de los estudios^{31, 19, 32, 33, 8} tienden a demostrar que ésta es más prevalente en niños y jóvenes adultos.

Los datos existentes parecen demostrar que, en países en desarrollo, la mayor incidencia de infección ocurre en niños menores de 5 años³ mientras que otras poblaciones, el número mayor se encuentra en las personas de 5 a 34 años.⁹

Existe una proporción de 3:2 de varón a hembra hasta los 14 años, nivelándose de 1:1 entre las edades de 15 y 54 años para hacerse más frecuente en mujeres luego de los 55 años.

La homosexualidad en hombres se ha sugerido aumenta el riesgo de infección por campylobacter.³⁰

Finalmente, esta enfermedad aumenta su incidencia según nos acercamos al trópico o nos acercamos a los meses calurosos del año.8

Tratamiento

El tratamiento de la enteritis causada por Campylobacter es un tópico controversial, pues no existen estudios controlados donde se demuestre la efectividad de la terapia antimicrobiana. ¹⁸ Sin embargo, se debe enfatizar que la mayoría de los pacientes tienen una enfermedad autolimitante y mejoran sin quimoterapia. Existe un estudio reciente, doblemente ciego, controlado, donde eritromicina no alteró el curso natural de la enfermedad si el paciente era tratado 4 a 6 días luego del comienzo de los síntomas. ³⁴ Sin embargo, el paciente que no responde a terapia de sostén o el paciente que desarrolla complicaciones, debe ser tratado con antibióticos. ³⁵ La mayoría de las cepas de *C. fetus ss jejuni* son susceptibles *in vitro* a antibióticos tales como eritromicina, tetraciclinas, clindamicina, gentamicina, nitrofurantoina y cloranfenicol. En general, este organismo es resistente a penicilina, las cefalosporinas, rifampin, trimethoprim y vancomicina. La susceptibilidad a metronidazole, ampicillin y trimethoprim sulfamethoxazole es variable. ³

La droga de elección es eritromicina en una dosis de 250mg cuatro veces al día para el paciente adulto, y 40mg/kg/día para el paciente pediátrico. La prevalencia de cepas resistentes a eritromicina varía de un 8% en

Suecia a un 1% en Canada.3

El paciente séptico, sin embargo, debe ser tratado con gentamicina intravenosa, aunque se han reportado casos autolimitantes o asintomáticos de bacteremias por *C. jejuni* que posiblemente no había que tratar. Es importante recordar que las cefalosporinas no tienen utilidad en el manejo de *Campylobacter*.

Abstract: Campylobacter jejuni has emerged as an important pathogen in humans. If appropriate culture medias are utilized, this organism may be recovered from the feces of patients with acute diarrhea at least as often as Salmonella or Shigella species. This organism has not only been associated to acute diarrhea or enteritis, but have been occasionally associated to erythema nodosa, endocarditis, meningitis, abortion and proctitis among other diseases. Clinical course is usually self-limited, and most patients recover in less than a week. Nevertheless, treatment with erythromycin should be considered for those patients in which prolonged, bloody diarrhea or high fever is present. Simplification of culture techniques now allow the diagnosis of campylobacter enteritis; therefore, C. jejuni should be sought routinely in fecal specimens of patients with diarrhea.

Reconocimiento

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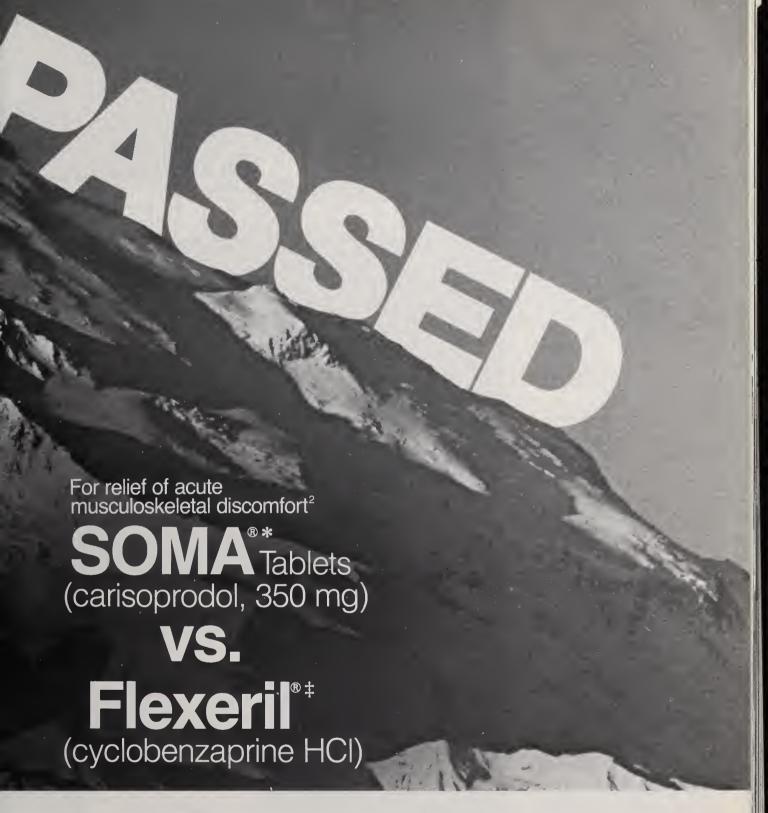
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ARTICULOS ESPECIALES

La Delincuencia Juvenil a Dieciseis Años del Siglo XXI

Luz M. Guevara de Ramos, M.D., FAACP

6 T Jivimos en una edad decadente; la gente ya no respeta a padres; son rudos e impacientes; frecuentan tabernas; no tienen auto control"; estas frases tal vez parecen de actualidad, sin embargo, fueron encontradas en escritos en la cultura Sumaria, datan de 3,000-4,000 A.C., 1 Comentarios parecidos referentes a los adolescentes se han repetido através de la historia en la literatura. En Puerto Rico, también ha preocupado el problema de la delincuencia juvenil. Este tema ha sido estudiado por las diversas disciplinas de las ciencias de la conducta.², ⁴ La aportación de la medicina a este problema ha sido limitada y poco efectiva. Durante las últimas décadas se han comenzado a identificar hallazgos alentadores para el diagnóstico y menejo del mismo. Estos estudios serán discutidos en este artículo.

El término delincuencia juvenil, tiene implicaciones legales. Trata de ubicar al menor que incurre en conducta delictiva o que no sigue las reglas establecidas. En Puerto Rico, la lev 97, denomina "indisciplinado" al menor cuyos padres, encargados o maestros no pueden controlarle y constituye una amenaza para su propio bienestar o el de la comunidad; se entiende legalmente que esta conducta es corregible. Estos casos son canalizados por las agencias de Servicios Sociales.

Se entiende por "falta", hechos cometidos por un menor, que de cometerlos un adulto constituirían un delito definido y penalizado por la ley. Esta situación es atendida por el Tribunal Tutelar de Menores. Dentro de los procedimientos jurídicos del Tribunal, se puede identificar o no la necesidad de una evaluación psicológica, social y médica (psiquiátrica y neurológica). Cuando se determina que el menor quede en libertad a prueba, éste deberá cumplir con unas reglas de conducta que establecen:

- 1. recluirse en el hogar a determinada hora.
- 2. abstenerse de frecuentar sitios donde se expendan bebidas alcohólicas.

- 3. asistir a la escuela o procurarse un trabajo para así mantenerse ocupado en horas laborales.
- 4. abstenerse de frecuentar sitios donde se celebren juegos prohibidos.

Se le asignará un oficial probatorio quien le evaluará y aconsejará. El Tribunal puede renunciar a la jurisdicción de un caso en determinadas circunstancias y trasladarlo al Tribunal competente para que el menor sea juzgado como adulto. La ley tiene la intención de proteger al menor y rehabilitarlo. Una vez cumplidos los 18 años el expediente se cierra y el menor adviene adulto libre de expediente judicial.

No obstante, resultaría interesante un estudio longitudinal que observe la conducta posterior en su vida adulta. ¿Cuántos cometerán otros delitos? Robins da seguimiento hasta la vida adulta a un grupo de niños con desorden de conducta.5, 6 Observa que en aquellos adultos que desarrollan personalidad antisocial, la repetida conducta antisocial en la niñez era el elemento más relevante. Los factores ambientales o sociales en que se desenvuelve el niño, no eran de por sí los mas prevalentes. Igualmente, encontró que los adultos que desarrollan alcoholismo también habían tenido desorden de conducta durante su

El diario San Juan Star en su edición del 30 de julio de 1984 informa un aumento en la criminalidad de un 15% sobre el año anterior. Se anticipa hasta un total de 100,000 crímenes serios, muchos relacionados al uso de drogas.7 El informe estadístico de la División de Ayuda Juvenil de la Policía de P.R. anota todos los años el total de faltas incurridas por menores. ¿Cuántos de estos menores estarán involucrados en el aumento de la criminalidad cometida por adultos? La División de Ayuda Juvenil es la agencia que entra en contacto con el menor que presenta problemas y donde se origina la querella. La querella en el caso del menor es el equivalente a la denuncia o acusación en caso de adultos. Esta división puede llevar la querella al Tribunal o canalizar el problema a otras agencias competentes dependiendo de la gravedad del problema a juicio de la policía. Durante el año 1981-82 llegó a la atención de esta División 10,764 casos.

Universidad de Puerto Rico, Recinto de Ciencias Médicas, Escuela de Medicina

Las disposiciones del Tribunal antes mencionadas muestran que la intención de la ley es buena. Se observa igualmente la dedicación del personal de Tribunal y de las otras agencias sociales ante su gigantesca tarea debido al creciente número de casos. ¿Tiene el Tribunal y las agencias pertinentes todos los recursos necesarios para cumplir su encomienda? La respuesta parece ser en la negativa.

¿A que riesgos se enfrenta nuestro adolescente? La distribución poblacional para la etapa de desarrollo que nos concierne se presenta en el censo de 1980 de la siguiente forma: (a) la población total de Puerto Rico es 3.1 millones.⁸ La población entre 10 y 19 años es de 675,425. Sólo el 5.8% entre las edades de 16 a 19 años trabaja, el 58% esta desempleado.

Durante la adolescencia los grupos de pares (compañeros) "peer" ayudan a que se re-estructure u organize la personalidad. Se debe anotar que no sólo se imita a los compañeros de la misma edad, sino que es necesario también imitar a otros adolescentes en una etapa de desarrollo superior quienes sean más independientes y tenga mayor desarrollo psicosexual. Por tanto los padres y maestros no deben prohibir este intercambio de edades en situaciones normales. También es un proceso facilitador la educación mixta de ambos sexos. ¿Cuál es el riesgo con los pares? Robles hizo un estudio longitudinal en 1975 sobre el uso de drogas lícitas e ilícitas en estudiantes adolescentes en las escuelas secundarias de Puerto Rico.^{9, 10} Se destaca que en aquellos estudiantes que utilizaban drogas, sus pares también las usaban. El 52.3% de los adolescentes informaron haber usado drogas (alcohol, cigarrillos, etc.) El 11% usó marihuana. El uso de drogas era más frecuente en escuelas privadas.

La aportación de la medicina ha estado limitada a las contribuciones de algunos estudios psiquiátricos y neurológicos. Aún dentro de estas especialidades se ha percibido cierto pesimismo ante el tratamiento poco eficaz del desorden de conducta y personalidad antisocial. ¿Qué sucede? ¿Es que no hay nada que hacer con los menores que comenten faltas o son indisciplinados?

La psiquiatría en las últimas tres décadas ha logrado avances hacia el entendimiento del aspecto biológico de la conducta humana. La tomografía computarizada se esta utilizando con frecuencia. Entre los estudios presentados se identifica anomalías anatómicas en algunos niños con dislexia; se observó el diámetro parieto-occipital posterior revertido. 11 Otro estudio, hecho por Youngerman y Canino señala la disminución de conducta agresiva en adolescentes varones tratados con litio. 12, 13 La utilización de los marcadores biológicos está bajo estudio. Uno de ellos es la medida en orina de 24 horas de 3- metoxi 4- hidroxifenolglicol (MHPG). Se observa el MHPG disminuido en los niños hiperactivos. 14 El metabolito del neurotransmisor serotonina (5HIAA) se encontró disminuido en pacientes agresivos. 15

En estudios recientes, Lewis evalua una población de adolescentes en una institución correccional.¹6 Sus hallazagos indican que aquellos menores que habían sido más violentos (homicidas, violadores, etc.) presentaban anomalías en EEG, signos neurológicos tales como movimientos coreiformes, Babinski, etc.) y síntomas psicóticos. Su ejecutoria académica era deficiente y

estaban atrasados en su ubicación de grado escolar. Se destacó el hecho de que habían presenciado o vivido violencia en su hogar. Una vez identificados sus problemas, aquellos que tenían enfermedades tratables mejoraron en su conducta.

¿Cuáles son algunos de los precursores de la conducta delictiva? La violencia doméstica aparece común.¹6 El maltrato a los menores y con golpes a la cabeza estaban posiblemente asociados a los hallazgos encefalográficos de Lewis.

Hay tres desórdenes psiquiátricos que se inician en la niñez y que pueden coincidir en algunos menores que luego delinquen. Estos son: los desórdenes de deficit en atención. los desórdenes de conducta y los desórdenes específicos del desarrollo relacionados al proceso de aprendizaje.

Uno de los más reconocidos estudios epidemiológicos psiquiátricos fue hecho por Rutter en la Isla de Wight, en Inglaterra. Encuentra que un tercio de los niños con problemas en la lectura, desa rrollan también desorden de conducta. 17, 18 Estos desórdenes se encuentran en todas las clases socioeconómicas, se sospecha que existen sin ser diagnosticados. La Universidad de Puerto Rico está realizando un estudio de prevalencia de desórdenes psiquiátricos en niños. Este estudio nos indicará cuáles son los problemas psiquiátricos más frecuentes de la niñez en Puerto Rico. 19

El desorden de deficit de atención puede presentarse con o sin hiperactividad. Cantwell tiene varios estudios en estas áreas. Esta condición es tratada con estimulantes simpaticomiméticos. Un 30% de los niños no responden a los mismos. Se esta estudiando un patrón encefalográfico que parece estar asociado a determinar la respuesta a la medicación. Se postula también una alteración en la trasmisión química neuronal. Muchos niños con esta condición, debido a su carencia de atención e hiperactividad, no pueden aprovechar el proceso de aprendizaje a cabalidad.^{20, 21}

Kupietz mide el nivel de metilfenidato (Ritalin) en el plasma de niños hiperactivos. Encuentra que a medida que el nivel plasmático de Ritalin disminuye, el niño comete más errores en sus tareas escolares.²² El desorden de déficit de atención puede desaparecer, mejorar o permanecer igual hasta la vida adulta. La medicación se utilizará junto a otras medidas terapéuticas según sea necesaria.

Los niños con desorden específico en el desarrollo de la lectura, escritura, aritmética o articulación se presentan también con dificulatad en el aprendizaje. Esto a pesar de tener algunos de ellos un nivel de funcionamiento intelectual brillante o mayor en algunas áreas. Este hecho hace que tanto padres como maestros se confundan al ver que el menor puede hacer unas tareas y parecer perezoso para otras. El proceso de evaluación de estos niños ha mejorado en los últimos años, requiere un esfuerzo multidisciplinario. Las pruebas educativas más conocidas como Wide Range Achievement Test, Grey e Illinois of Psycholinguistics aún no han sido estandarizados para nuestra población. Los niños que sufren este desorden pueden superar el problema con ayuda psiquiátrica y educativa.

Los desórdenes de conducta en los niños se manifiestan

desde los 8 años. Se caracteriza por violar las normas esperadas para su edad y no respetar los derechos de los demás. Puede o no mostrar afecto, empatía o apego a los demás. Su autoestima es pobre, a pesar de proyectarse como fuertes y poderosos. Estos desórdenes, cuando ocurren en los niños clases afluentes pudieran no llegar al sistema judicial dado los múltiples recursos a nivel privado.

Puig-Antich trató un grupo de niños que presentaban desorden de conducta con Imipramina.²³ A estos niños se le diagnosticó un desorden afectivo concurrente. Se observó mejoría en su conducta luego del tratamiento con antidepresivos y se mantuvo la misma una vez cesada la medicación.

La retardación mental y los desórdenes esquizofrénicos, u orgánicos pueden estar asociados a conducta delictiva. Las técnicas de C-SCAN, PET, etc, también están siendo desarrollados para la identificación de estas condiciones. En este trabajo no se hace énfasis en estos desórdenes por ser su prevalencia menor (1%).

La Academia Americana de Pediatría ha recomendado a sus miembros evaluar los hábitos recreativos de los niños. Preocupa en especial el impacto de la violencia en los medios noticiosos tales como la televisión.²⁴ Murray luego de 25 años de investigación señala que los niños aprenden nuevas formas de agresión en los programas televisados. Igualmente, menciona la inmutación de los niños ante la violencia, luego de observar la misma repetidamente.²⁵

Discusión

Los estudios señalan que no se trata de un problema que obedezca a un sólo factor en particular. La combinación de factores biológicos, psicológicos y sociales están presentes en el ofensor juvenil. El número de casos que llega a la consideración del Tribunal Tutelar de Menores ha disminuido. Por otro lado, el número de casos que reciben la atención de la División de Ayuda Juvenil de la Policía de Puerto Rico ha aumentado. ¿Son los adolescentes más vulnerables a sufrir condiciones de riesgos antes mencionados los que llegan al Tribunal? El Tribunal no cuenta con los suficientes recursos evaluatipara contestar individualmente este interrogante.

Los menores que son enviados por el Tribunal a un hogar de detención (instituciones correccionales) no están recibiendo servicios de evaluación y tratamiento individualizado que requieren. Las experiencias de los menores dentro de estas instituciones han sido descritas.² Los menores recluidos en estas instituciones están sujetos a un sistema disciplinario inconsistente. Llamó la atención a Palau y Ruíz la ausencia de sentimientos positivos en los menores. Se describe la homosexualidad desde la perspectiva de la situación institucional.

Otero coincide con las obserciones de Lewis. Señala a la delincuencia juvenil relacionada al aumento en la deserción escolar.

Cabe mencionar aquí el dato censal de 1980, donde se indica que en Puerto Rico un 11.5% de las personas mayores de 18 años no saben leer ni escribir. Siendo la educación compulsoria hasta el 8vo grado y existiendo la

escuela nocturna hace varias décadas, es este dato digno de preocupación y análisis. ¿Será tal vez parte de esta población la que tuvo problemas de aprendizaje que no se identificaron? El médico debe en su historial preguntar por: aprovechamiento académico, signos tales como problemas con la lateralidad, inversión de símbolos ∃ por E o δ por 5, y problemas de déficit de atención. Todo ésto con un funcionamiento intelectual normal.¹⁰ Es la responsabilidad del médico preguntar e identificar la violencia doméstica hacia la madre y los niños. El niño que tiene déficit de atención y éste le represente problema, debe ser medicado. La maestra debe ser informada. Cuando se identifique otro desorden mental el mismo deberá ser tratado con la medicación específica, bien sea antipsicótico, antidepresivo o estabilizador del afecto. La familia también será atendida según sus necesidades.

Nos planteamos aquí: ¿para qué educamos a nuestros niños? ¿Qué oportunidades le ofrecemos? Hay diversos programas vocacionales hacia los cuales son dirigidos. Una vez finalizados estos. ¿qué? La población desempleada para estas edades de 16 a 19 años es de 58.1%. Las interrogantes son las siguientes: ¿Se podrá enseñar principios básicos de economía, mercadeo, etc., desde los primeros grados? Será entonces posible que estos niños desarrollen unas industrias escolares, a pesar de las limitaciones en la tecnología a su nivel escolar. Pueden las leyes del trabajo permitir estas empresas antes de que el adolescente salga de su adiestramiento vocacional. Permitirá el ámbito industrial este desarrollo. Lo apoyará, ofrecerá empleos?

Conclusiones

La indisciplina en los menores ha sido una preocupación evidenciada desde tiempo inmemorial. Las posibles causas han sido analizadas desde diferentes perspectivas. En Puerto Rico, desconocemos la magnitud del problema de la violencia y como se relaciona este con nuestra juventud. Procede continuar estudiando el problema que constituye la delincuencia juvenil en la esperanza que lograremos señalar las causas precisas, el tratamiento indicado y la prevención para el año 2,000. Para esto debe ponerse a la disposición de los profesionales los recursos necesarios. Mientras tanto debemos aunar esfuerzos para la mejor utilización de los hallazgos en los estudios que se han realizado hasta esta década del ochenta.

Summary: Juvenile delinquency has been present in all societies. The possible causes have been analyzed from different points of views. In Puerto Rico, the relationship of violent crimes to juvenile delinquency is unknown. The precise causes, treatment and prevention for the 21st century should require research efforts. During the eighties a multidisciplinary approach is needed to utilize the current knowledge to deal with the juvenile offender.

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So do we.





Los Potenciales Evocados en Boxeadores Antes y Después de un Combate

Juan Rodríguez del Valle, M.D.

Hace cuatro años, después de presenciar un combate de boxeo, surgió la idea de este proyecto. La tarea no fue fácil, pero luego de varios años de trabajo y sacrificio pudimos lograr superar todos los inconvenientes y ver realizado nuestro proyecto de investigación.

Se hizo un protocolo de preguntas del historial del boxeador y de sus familiares. Se hizo énfasis en el historial de epilepsia cefaleas, locura, número de peleas y veces que habían sido noqueados.

El proyecto consistió en practicarle estudios de potenciales evocados cerebrales en sus tres modalidades: visual, auditiva y somatosensorial, antes y después de una pelea a estos boxeadores.

Las peleas estaban pactadas para un día cada semana y se escogían para el estudio dos boxeadores por semana. El Sr. José Luis Vellón (entrenador) escogía los dos boxeadores que él entendía podrían tener más acción. Durante la semana se les practicaban los estudios y el sábado por la mañana se les volvían a repetir de la misma forma.

El propósito de este estudio era intentar probar si los golpes que reciben de una forma repetida estos boxeadores en la cabeza, pueden causar daños al sistema nervioso central y de causarlos, si éstos son reversibles o irreversibles. Pensamos que al hacer estos estudios antes de cada pelea, además de ofrecer un dato comparativo, nos proveería evidencia de compromisos previos al sistema nervioso no detectados.

Materiales y Métodos

La serie incluye solamente diez boxeadores pero la misma está en un proceso de ampliación y se proyecta hacer un seguimiento de los ya estudiados.

La modalidad somatosensorial se practicó a 40 milisegundos, la auditiva a 10 milisegundos y la visual a 250 milisegundos. Las edades de estos boxeadores fluctuaron entre los 16 y 20 años, cinco de ellos con 18 años. El promedio de peleas efectuadas por cada uno de ellos fluctuaban entre 9 y 59. La mayoría entre 20 y 30 peleas.

Dos de ellos sufrían de dolores de cabeza, ninguno de epilepsia ni de locura. Los dos que sufrían de cefaleas tenían antecedentes familiares de cefaleas. Uno de ellos indicó que su padre estaba incapacitado debido a un "padecimiento nervioso". Cuatro de ellos habían sufrido un "Knock out" en su carrera. Los demás no tenían antecedentes de haber sido noqueados. Todos eran maniderechos.

Resultados

Los *estudios auditivos*, tomando como base el estímulo de 75 decibeles arrojaron lo siguiente:

- Aumento de la latencia de la onda V en los estudios posteriores a la pelea en cinco de los diez boxeadores estudiados.
- En tres de ellos no encontramos aumentos y en dos de ellos por causas desconocidas los estudios demostraban alteraciones eléctricas antes de las peleas, las cuales no se encontraron posterior a ellas.
- En el oido izquierdo se encontró aumento en cinco de los sujetos y cuatro en el oido derecho. Los aumentos fluctuaron entre 0.04 y 0.2 milisegundos en ambos oidos.
- Se encontró aumento de las latencias entre ondas I y V en estos mismos sujetos en cinco de ellos en el oido izquierdo y en cuatro de ellos en el oido derecho. Fluctuaron los aumentos entre 0.04 y 0.4 milisegundos. La distancia entre las ondas III y V se aumentó en tres de ellos en el oido derecho y sólo uno en el oido izquierdo.

Los estudios somatosensoriales nos dieron el siguiente resultado:

• Cuatro sujetos demostraron alteraciones con aumento de las latencias después de la pelea en las ondas N19 y P22, fluctuando estas diferencias entre 0.64 y 5.92 milesegundos. Uno de ellos tuvo diferencias al estímulo del nervio mediano derecho solamente. Los demás sujetos no demostraron alteraciones de importancia.

Los estudios visuales demostraron:

• Alteraciones de aumento de latencias de las ondas N70 y P100, después de las peleas en cinco sujetos. Fluctuaron estas diferencias entre 2 a 17 milisegundos.

Respecto a la intensidad de los golpes recibidos y las alteraciones encontradas, vemos que cuatro de ellos tuvieron peleas "suaves" donde no recibieron golpes contundentes y repetidos. Dos de ellos no tuvieron alteraciones en ninguno de los estudios, uno tuvo alteraciones en el auditivo solamente y el otro en los visuales y somatosensoriales.

• De los restantes seis que recibieron castigo en sus peleas, cuatro de ellos demostraron alteraciones en las tres derivaciones, uno presentó en el auditivo solamente y el sexto no presentó alteraciones en ninguna de las derivaciones.

Conclusión

Los estudios hasta este momento, demuestran que las alteraciones eléctricas encontradas guardan cierta relación con el castigo que reciben estos boxeadores. Los potenciales evocados cerebrales son un método de investigación neurofisiológica que ayudan grandemente en la evaluación de estos atletas. Creemos que por este medio podemos determinar los daños que reciben los boxeadores en su cerebro y se podría determinar si estos boxeadores están médicamente aptos para continuar practicando ese deporte aunque las diferencias encontradas en estos boxeadores no son del todo concluyentes.

Los estudios fueron hechos con boxeadores aficionados, jóvenes que todavía no han recibido mucho castigo, que usan protectores en la cabeza y que los jueces tienden a protegerlos cuando llevan la peor parte del combate.

Sería de gran valor científico el poder hacer estos estudios con boxeadores profesionales que reciben castigo a mansalva, de forma despiadada, y sin control alguno.

Agradecimiento

Deseo por este medio hacer un reconocimiento al Sr. José Luis Vellón por la gran ayuda prestada en la realización de este proyecto, a todos los boxeadores que desinteresadamente prestaron su cooperación y al presidente de la Federación de Boxeo Aficionado de Puerto Rico.

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Fingers flat, move opposite hand gently over each breast. Check for lumps, hard knots, thickening.



2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.





DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., FACC* Amalia Martínez-Picó, M.D., FACC* Frances Colón Vega, M.D.*

Un joven de 13 años de edad se hospitaliza para un cateterismo cardíaco electivo. En su historial médico se destaca la presencia de un soplo cardíaco desde el período neonatal que cursó sin complicaciones. Este soplo fue aumentando en intensidad y duración luego del período pre-escolar, pero el paciente nunca tuvo síntomas de etiología cardíaca. Su crecimiento, desarrollo y tolerancia al ejercicio siempre fueron normales.

El examen físico al hospitalizarse demostró un adolescente bien desarrollado con signos vitales normales y sin cianosis. Tenía un precordio silente, con un PMI en el 5° espacio intercostal izquierdo al nivel de la línea medio-clavicular. Se palpaba un frémito en el 3er. espacio intercostal izquierdo cerca del reborde esternal y había accesibilidad ventricular derecha. A la auscultación se apreció un soplo eyectivo, sistólico, prolongado, rudo, grado IV/6 audible mejor en los espacios intercostales izquierdos 3 y 4 con irradiación por todo el precordio y la espalda. No había arrastre diastólico ni sonido de eyección ("click"). El S_1 era normal, el S_2 tenía un desdoblamiento normal, variable con la respiración y un componente pulmonar (P_2) disminuido. No había S_3 , S_4 , ni ritmo de galope. Los pulsos periféricos eran normales en todas las extremidades.

El electrocardiograma cumplía con los criterios de hipertrofia ventricular derecha y el eje eléctrico de QRS demostraba una desviación a la derecha (+ 100°). En la radiografía de tórax se podía apreciar una silueta cardíaca de tamaño y configuración normal al igual que la circulación pulmonar.

En la figura 1 se ilustra una vista lateral del ventriculograma derecho que se le hizo al paciente y la figura 2 es una vista de su arteriograma pulmonar.



Figura 1. Ventriculograma derecho en posición lateral.



Figura 2. Arteriograma pulmonar en posición anteroposterior. Levofase.

¿CUAL ES SU DIAGNOSTICO?

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Diagnóstico

- Estenosis pulmonar valvular
- Retorno venoso anómalo parcial

La estenosis pulmonar valvular representa una obstrucción congénita a la salida del tracto ventricular derecho. Puede existir de forma aislada, asociada a estenosis pulmonar a otros niveles (infundibular; supravalvular), a estenosis anular o a otras cardiopatías, siendo la comunicación interventricular la más frecuente. La estenosis pulmonar valvular con septo interventricular intacto es un defecto cardíaco frecuente. Se dice constituye un 8-10% de las cardiopatías congénitas en la edad pediátrica.¹, ² De acuerdo al grado de obstrucción que cause esta valvulopatía se producirán diferentes manifestaciones clínicas según la obstrucción sea leve, moderada, o severa.

Los pacientes con estenosis pulmonar y septo interventricular intacto donde el grado de obstrucción es leve o moderado suelen cursar asintomáticos. La aparición de síntomas tales como disnea tras el esfuerzo, dolor precordial, cianosis luego del ejercicio o mareos, traducen una obstrucción significativa y que ya probablemente sea severa.

El hallazgo clínico más significativo en la estenosis pulmonar con septo intacto es la presencia de un soplo sistólico-eyectivo, rudo, con mayor intensidad en el borde esternal izquierdo superior. Este soplo se irradia por todo el precordio, cuello y espalda. Fonocardiográficamente tiene una configuración "crescendo-decrescendo" con un punto de mayor intensidad meso o telesistólico y usualmente es de media o alta frecuencia. En la estenosis pulmonar leve el soplo es corto y su "pico" no sobrepasa la mesosístole. Según la estenosis va progresando en severidad el soplo se va prolongando y cuando la obstrucción es ya severa el soplo puede sobrepasar el componente aórtico del segundo sonido.

El "click" eyectivo de la estenosis pulmonar valvular también sufre alteraciones según progresa la obstrucción. Este "click" se produce por la apertura súbita de la válvula pulmonar estenótica pero aun flexible, y no por la expansión súbita de la pared de la arteria pulmonar como se pensaba antes.⁴ El click aparece temprano en sístole, y en la estenosis pulmonar valvular leve puede separarse del S₁ por más de 0.04 segundos y oirse en el precordio superior a lo largo del reborde esternal izquierdo. Usualmente aumenta durante la espiración. Según la severidad de la estenosis valvular progresa, el intervalo S-1 click se va disminuyendo hasta que este sonido de eyección va desapareciendo a la auscultación. El intérvalo A2 -P2 se va alargando según aumenta la severidad de la estenosis pulmonar, al igual que el P₂ va disminuyendo en intensidad.

La estenosis pulmonar queda claramente demostrada con un ventriculograma derecho, sobretodo en la vista lateral donde puede definirse mejor la morfología de la válvula. Tras la inyección del material de contraste puede verse el "jet" del contraste pasando através del orificio valvular estenótico y el engrosamiento de las valvas. (Fig. 1) El caso que se presenta tenía un gradiente sistólico (en reposo) de 75mmHg. através de la válvula, lo que se considera una estenosis pulmonar moderada a severa.

En la figura 2 puede apreciarse como el retorno venoso pulmonar de este paciente es parcialmente anómalo. Podemos observar como las venas pulmonares derechas y la inferior izquierda (identificadas con las flechas) drenan normalmente al atrio izquierdo (LA). Sin embargo la vena pulmonar superior izquierda (LSPV) drena por medio de una vena vertical (VV) a la vena innominada izquierda (Inn.v.) y esta a su vez lo hace a la vena cava superior (SVC). Las anomalías de drenaje venoso anómalo no son muy frecuentes y cuando el defecto es parcial, usualmente lo es por drenaje anómalo al lado derecho, principalmente a la vena cava superior y casi siempre están asociadas a defectos del septo interatrial. Sara vez coexisten con un septo interatrial intacto como lo fue nuestro caso.

Por lo regular el drenaje anómalo de una sola vena pulmonar no es clínicamente aparente. Cuando esto sucede el drenaje anómalo es apenas un 20% del flujo pulmonar total lo que es hemodinámicamente insuficiente para tener consecuencias clínicas significativas.⁶

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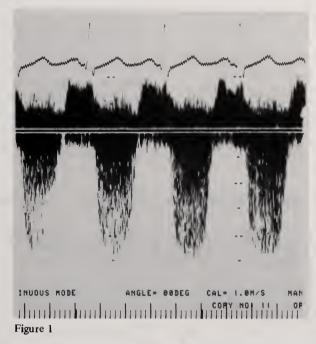


ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., FACC* Gerald R. Marx, M.D.**

Hugh D. Allen, M.D., FACC**

This 27-year-old male underwent mitral valve replacement with an Ionescu-Shiley bovine valve, #33, on January 1984. He is presently asymtomatic and working. However, a long apical murmur is heard.



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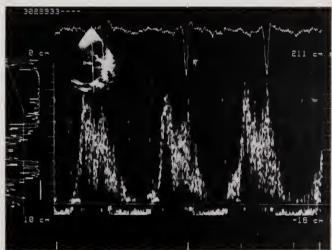


Figure 3

Questions

What is the diagnosis?
What is the severity of the lesion?

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Answers

Mitral Regurgitation (MR) of a bioprosthetic mitral valve.

Figures 1 and 2. Irex continuous wave (CW) Doppler tracing, with angled probe from apical position. Prominent systolic negative mitral regurgitant jet, away from transducer.

Peak velocity (V) = 4.8 M/S, mean 199 cm/S. Using modified Bernoulli equation, 4 V^2_2 , the pressure drop across mitral valve from left ventricle to left atrium (LA) = 4 x (4.8)² = 92 mm Hg. Abnormal diastolic velocities are also noted.

Figure 3. Honeywell freeze-frame print from pulsed Doppler tracing of mitral outflow. A 2.25 MHZ transducer was used. Apical 4-chamber view with sample volume (SV) placed in the left ventricular inflow tract (LVIT) or mitral ourtflow (see left upper 2-D insert for SV position). Mitral peak flow V = 1.8 M/S mean 64 cm/S

Mitral valve peak gradient at one point during early diastole (D wave) = $V^2_2 = 4 \times (1.8)^2 = mm$ Hg.

Pressure half-time = V

$$\frac{\text{to}}{2} = \frac{1.8 \text{ M/S}}{1.41} = 1.28 \text{ M/S} = 83 \text{ mS}.$$

Mitral valve area = $\frac{220}{83}$ = 2.6 cm².

Pulmonary artery (PA) flow (not illustrated)- peak V 77 cm/S, mean 24 cm/S; diameter 2.69 cm; PA flow 8092 cc/min.

Time-to-Peak velocity = 150, 140, 130 ms, which is normal.

Discussion

Doppler echocardiography in MR, with the sample volume in the LA may reveal the following:

- 1) In MR systolic turbulent flow is present with spectral dispersion and broadening; multiple high frequencies are present; aliasing is present in pulsed Doppler tracings and obviates accurate measurement; CW Doppler or high pulse rate frequency (PRF) should be used; the insufficient jet may be only late systolic in mitral valve prolapse; it may be bidirectional when left parasternal view is used. Views for assessment of MR are: apical 4- and 2-chamber, parasternal, subcostal, transesophageal.
 - Normal: only diastolic mitral flow and no systolic flow is present.
- 2) V of antegrade mitral flow is increased. A small negative systolic wave may be present on the LVIT trace. The LA is the location of the jet and is where interrogation should take place.
- 3) Predominant early aortic high blood flow volume.
- 4) Blowing, raspy, high pitched sound.
- 5) Grading the severity mapping the LA for spatial diffuseness of turbulence; amplitude and with of negative systolic wave the more likely is MR.
- 6) Predominant MR produces an equally increased initial mitral flow V as does MS, but with a rapidly

- descending slope. The pressure half-time helps distinguish MR from MS: in MR the mean is 50, range 35-80 mS.
- 7) Distinguish MR from the diastolic-systolic laminar flow from pulmonary veins (especially in children and high flow states).

Doppler echo shows high specificity and correlation with angiography, and can even detect inaudible or atypical MR; it may outperform auscultation; phonocardiography may give an incorrect result. It shows high sensitivity and specificity in evaluating prosthetic and bioprothetic valve insufficiency and malfunction. It may be more sensitive than an experienced cardiologist or routine echocardiography. 2-D and M-mode echo are limited in Ithe evaluation of valvular regurgitation, but 2-D echo is useful for placement of the SV.

The LA pressure may be estimated in the presence of MR as follows: Right arm cuff systolic pressure (120/90 mm Hg) equals left ventricular (LV) systolic pressure in the absence of LV outflow obstruction (normal velocity). The LV-LA systolic gradient = $4 \text{ V}^2 = 4 \text{ x} (4.8)^2 = 92$; the difference between systolic arm (LV) pressure and the gradient = LA pressure in systole, = 28 mm Hg.

The Ionescu-Shiley mitral valve has a surface area by catheterization of 2 cm², and a resting gradient of 4 mm Hg. The orifice area appears to be 2.5 cm² (orifice to margin diameter and area ratio of 0.76), suggesting no significant prosthetic valve obstruction. The mitral gradient of 13 mm Hg may be attributed to the flow of MR; moreover, the pressure half-time is only slightly prolonged.

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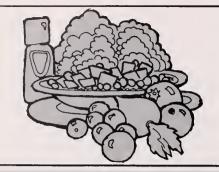
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MEDICAL ASPECTS OF NUTRITION

Caffeine*

Caffeine is one of a group of compounds called methylxanthines that occur naturally in about 63 species of plants, including coffee beans, cocoa beans, cola nuts and tea leaves. It is thus naturally present in coffee, tea, cola soft drinks, cocoa and chocolate. It also is added as a flavoring agent in some foods and beverages, including cola and pepper-type soft drinks as well as some noncola soft drinks.

The amount of caffeine per serving varies with the type of product. The caffeine content per 5-ozcup is about 64-150 mg for drip or percolated coffee, 40-108 mg for instant coffee, 2-5 mg for decaffeinated coffee, 9-50 mg for brewed tea and 12-28 mg for instant tea. Although tea and cocoa contain less caffeine than coffee, they also contain related chemicals.

Other factors significantly affect the amount of caffeine per serving of coffee or tea. They are the variety of coffee bean or tea leaf, where it was grown, the particle size (the coffee "grind" or tea leaf "cut") and the method and length of brewing or steeping. The amount in cocoa and chocolate is considerably less variable but still depends upon the origin of the beans and other factors.

Soft drinks range from 0 to 60 mg of caffeine per 12-oz serving. Because soft drinks are subject to strict quality controls and consistency requirements, the amount of caffeine in a particular soft drink is uniform from can to can and bottle to bottle.

Caffeine also serves a variety of pharmacologic functions and is found in combination with drugs used as stimulants, pain relievers, diuretics, cold remedies and weight-control products.

Physiological Effects

Caffeine stimulates the central nervous system and can produce a variety of effects elsewhere in the body. Depending upon the dose, it can increase hearbeat and basal metabolic rate, promote secretion of stomach acid and step up the production of urine. It acts to dilate some blood vessels, to constrict others and to increase the capacity for muscular work. Subjectively, the overall

effect ofthen has been described as a "lift," a feeling of being wide-awake and able to focus on mental and manual tasks. Typically, however, caffeine will only "lift" a person back to his or her original condition before sleeplessness, fatigue or boredom-degraded normal performance.

Caffeine in the blood plasma rises to peak levels within 30 minutes of consumption by mouth. While it is present in the blood, caffeine also penetrates all the body's tissues in amounts approximately proportional to their water content. It freely crosses the blood/testicular and fetal/placental barriers and also is absorbed into human milk

The half-life of caffeine—the time required for the body to eliminate one-half the amount introduced—varies from several hours to several days, depending upon age, sex, hormonal status, medication being taken and whether an individual smokes. It ranges from less than 3 hours in children and smokers, about 3 to 7 hours in nonsmokers, up to 13 hours in women on the "pill", and 18 to 20 hours in pregnant women, particularly in the last trimester, to about 3 to 4 days in newborns.², ³, ⁴, ⁵, ⁶

There is no persuasive evidence that moderate amounts of caffeine are harmful to the average healthy adult. However, excessive consumption (more than 1,000 mg—the equivalent of about 10 cups of strong-brewed coffe—per day) may lead to anxiety, restlessness, delayed onset of sleep or frequent awakening, diarrhea, headache and heart palpitations. In addition to individual differences, the effects of caffeine seem to vary according to the amount consumed.

Questions of Safety

Caffeine received Generally Recognized As Safe (GRAS) status from the Food and Drug Administration (FDA) in 1958. In 1978, the Select Committee on GRAS Substances (SCOGS) reviewed the available data for FDA and concluded that "no evidence in the available information on caffeine demonstrates a hazard to the public when it is used in cola-type beverages at levels that are now current and in the manner now practiced." However, the committee recommended that additional studies be conducted.⁸

At various times since then, foods and beverages containing caffeine have been associated publicly with a

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wide variety of conditions and diseases. Some of the concern about the safety of caffeine is based on results of animal tests. There are many similarities between laboratory animals and man which make animals useful indicators of potential hazards to man. On the other hand, there are also major differences in physiology, metabolism and nutritional requirements that limit the extent to which information from animal tests can be extrapolated to humans.9

Animal test data clearly show that in very large doses caffeine can have deleterious effects (see Birth, Development and Growth). In human experience, there is little data on the effects of comparably large doses, but all of the available data on moderate intake of caffeine indicate

that the hazard to man, if any, is minimal.

• Ulcers. Coffee has been shown to stimulate the gastric mucosa and increase secretion of stomach acid, exacerbating existing ulcers. However, since decaffeinated coffee actually increased the flow of stomach acid more than regular coffee, it appears that caffeine is not the component of the brew that is responsible.

• Heartburn. Heartburn occurs when the ring of muscles at the lower end of the esophagus (the sphincter) relaxes, allowing the contents of the stomach to "back up" into the esophagus. Anything that makes these muscles relax can cause heartburn. Caffeine alone has virtually no effect on this sphincter. Coffee, however, has been shown to relax the sphincter in some people but to

have the exact opposite effect in others.

- Cardiovascular Disease. A study of 13,000 patients statistically linked coffee drinking with "heart attack" (acute myocardial infarction), with the greater the amount consumed, the greater the risk. 10, 11 These findings ran directly counter to the results of a number of other investigations, most notably the Framingham Study.¹² In this ongoing study of more than 5,000 men and women, followed for 22 years, no evidence of a relationship between coffee consumption and coronary heart disease, angina pectoris or myocardial infarction has been found.13
- Cancer. A link between bladder cancer and caffeine (as coffee) was first reported in the late 1960s and early' 70s, but a later study presented evidence that those studies did not actually demonstrate causation. 14, 15, 16 Subsequent studies have shown indirect associations but no cause-and-effect relationships and no dose-response relationships. 17, 18

A 1981 study reported an increased risk of pancreatic cancer among patients who drank coffee but a slightly decreased risk of bladder cancer among those who drank tea.19, 20 The results were statistically insignificant and other studies have failed to confirm them. 21

The largest study to date evaluated about 16,000 subjects over an 11-year period and showed no relationship between coffee drinking and cancer incidence at any site, including the pancreas and bladder.22, 23

The 1978 SCOGS review revealed no evidence that

caffeine was carcinogenic.8

• Fibrocystic Breast Disease. In 1979, a physician reported a link between consumption of methylxanthines and benign fibrocystic breast disease, based on a study of 47 female patients.24; 25 He reported that the increase in

risk was proportional to the amount of caffeine consumed.

In 1981, another physican reported a modest positive association between coffee and tea consumption and fibrocystic breast disease and breast cancer in a study of 451 women, but the data showed no apparent correlation between dose and response.26 A subsequent clinical trial indicated that women with fibrocystic disease who had abstained from methylxanthines experienced a statistically significant reduction in palpable breast findings, but the authors concluded that "the change was minor and of little clinical significance," and that there was no relation between clinically palpable breast finding scores and caffeine consumption levels.27

The largest study on the subject, involving 323 female patients and 1,458 controls, indicated no association between consumption of methylxanthines and fibrocystic disease.28

• Birth, Development and Growth. Largely on the basis of animal tests, FDA, in 1980, advised pregnant women to reduce their intake of caffeine.²⁹ In those tests, pregnant rats that were force-fed by stomach tube had offspring with missing toes or parts of toes. Birth defects were seen at the highest dose levels used in the study—the human equivalents of 56 and 87 cups of strong-brewed coffee per day—but not at lower dosages of 4, 8, and 28 cups per day.

Because the force-feeding method gave the animals their entire daily dose of caffeine at once, FDA sponsored a set of "sipping studies" in which rats received caffeine at similar daily dose levels but in their drinking water, a method more comparable to the way humans normally consume caffeine. Offspring of these rats did not show the same malformations seen in the offspring of the forcefed rats.30

These animal experiments, and more than 40 earlier studies, provide evidence that caffeine can indeed cause birth defects in animals at very high doses.

What Do Human Studies Show?

No associations have been found, during the past decade, in at least eight studies dealing with the incidence of birth defects in children and caffeine consumption by their mothers. In one study of more than 12,000 mothers. no relationship was found between coffee consumption and low birth weight, short gestation or any excess malformations among their babies.³¹

In another study, 2,030 infants were examined for a relationship between their mother's caffeine intake during pregnancy and six specific birth defects.³² The findings were negative, and the authors concluded that "coffee consumption has a minimal effect, if any, on incidence of birth defects."

Thus, there is no conclusive human evidence at this time to prove that moderate caffeine consumption by pregnant women causes birth defects. Moderation in the consumption of caffeine-containing foods, beverages and drugs, however, should be emphasized, especially during the third trimester, when caffeine is metabolized more slowly.

Alternative to Caffeine

Food manufacturers in recent years have introduced a number of caffeine-free colas, decaffeinated teas, caffeine-free herbal teas and improved versions of decaffeinated coffees. These alternative products are not necessarily more risk-free than their caffeine-containing counterparts. For example, there are conflicting data from animal studies on the safety of various solvents used to decaffeinate coffee. Most researchers agree, however, that the risks, if any, are low.

Although herbal teas do not contain caffeine, they do contain many other components that have not been subjected to as much scientific scrutiny as has caffeine. Many of these are probably harmless, but others have been shown to have a variety of toxic effects, even when used in moderate amounts.

While many questions about the ultimate safety of caffeine remain to be answered, the available data indicate that mankind will suffer no harm by consuming currently available caffeine-containing beverages in moderation.

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Discurso de Toma de Posesión del Presidente de la Asociación Médica de Puerto Rico Dr. José A. Nuñez López

La visión del mundo, de su gente y sus cosas depende de la persona que ve, de lo que ha visto y vivido. De cuándo y dónde está tratando de ver y de cómo ha conservado la capacidad de ver y no sólo mirar. Por eso nuestra Asociación ante un qué, cuándo y dónde tan cambiante en el sector salud, tiene que proyectarse hacia nuevos horizontes. Quisiera hoy compartir con ustedes mi visión de estos nuevos horizontes.

Pero... comencemos con la persona que ve. Inicie mi vida profesional en una institución total. En el hospital de psiquiatría. Participé en la creación de un cambio radical dentro de la institución y colaboré en muchos de los grandes logros de la psiquiatría a la comunidad en los años 60' para luego ver perder muchos de estos logros por falta de continuidad de esfuerzos, recursos adecuados y una politización excesiva.

Después de una experiencia de esta naturaleza, ¿Qué hacer? Que hacer si siempre en servicio público, para lograr los objetivos trazados, nos hará falta gente dedicada, tiempo razonable, recursos adecuados y propósito común. ¿Qué hacer? Concentrarme en mis problemas, en mi familia, mis cosas, o tratar de canalizar mi vocación de servicio hasta organizaciones profesionales voluntarias y tratar de ayudar a que una de estas, nuestra Asociación díese el ejemplo de lo que es una institución libre y democrática. Una institución que vive dirigida principalmente por sus principios, su filosofía, su visión de una noble tradición de compasión, altruismo y servicio al Pueblo.

Gracias a que pude encontrar compañeros que compartían valores y sentimientos iguales, comenzamos a través de participación ámplia, intensa, a introducir cambios a nuestra Asociación para que la misma respondiese al nuevo ambiente de salud de nuestro pueblo. Mas la tarea no ha sido fácil y está hoy en sus comienzos.

Vivimos en un país profundamente dividido. En un país durante la última década la gente, nuestra gente, no ha podido decidir con claridad que dirección quiere seguir. No ha podido ofrecer un mandato claro, definitivo a sus líderes.

Un país que durante los últimos años ha caído en actitudes que nos llevan a apreciar al listo, al que tiene espuelas, las tiene largas y tiene mollero y lo usa en forma aplastante... y se aprecia a éste, por encima del honesto, sincero, justo, vertical, que no se inclina. El que por sobre todo, quiere a su institución y respeta a su gente, su pueblo. Donde se aprecia el dinero, no como una medida parcial y temporera de un éxito relativo en algunas áreas de funcionamiento, sino como un fin en sí. Como un

medio de demostrar lo superior que somos al hermano puertorriqueño. Un país que la palabra crisis, ha perdido sentido. La palabra increíble, se usa con tanta frecuencia que ya se dice sin emoción, sin sentimiento. El vocablo definitivamente, se usa con el solo propósito de callar el diálogo. Este, es el dónde y cuándo estamos viendo.

¿Qué hacer? Si ante todo esto, sin embargo, se nos presenta una oportunidad única. Pues ante el deterioro de nuestras instituciones. Ante la desconfianza del pueblo por su gobierno. Ante la duda de que podamos nosotros dirigir nuestro destino. Estamos frente a un pueblo, que ya comienza a reaccionar, a dios gracias. El pueblo esta cansado de ver nuestros líderes criticarse los unos a los otros. Está cansado de la generalización y el exceso con que se usa el sistema de adversarios para la búsqueda de la verdad. El pueblo esta cansado, de que nuestros hombres quieran hacerse grandes, haciendo a los demás pequeños. Nuestra Asociación tiene que dar el ejemplo. Un nuevo estilo, un renacer verdadero. Tiene que traer liderato fresco, abierto, sincero, inteligente, pero sobre todo humano. Un liderato que busque el apoyo por convencimiento y no por servidumbre, lealtad incondicional o miedo.

Tenemos que presentar un modelo, un ejemplo, y podemos pues somos la institución que representa los profesionales que han dedicado su vida, a la noble tarea de aliviar el dolor y traer esperanza al hermano puertorriqueño. Al hermano que siente la amenaza de perder lo que más aprecia, su vida. Sobre todo, nos prepararon para servir a todos los puertorriqueños por igual, siendo esta una misión única, que nos convierte en privilegiados, instrumentos únicos de nuestro señor. No hay otra asociación que tenga el potencial nuestro para dar un ejemplo. Presentar un modelo de lo que es una institución profesional, libre y democrática. Dedicada a servir a todos por igual. Tenemos que ser ejemplo a través de los servicios a nuestros socios, a la comunidad que cuidamos y sobre todo a nuestro pueblo.

Servicio a los Socios

Para dar, hay que saber quién necesita, qué necesita, cuándo, dónde y cómo nos ven los que van a recibir algo de nosotros. Empecemos por el cuando y donde.

Estamos conscientes del escepticismo sobre el valor del cuidado médico, que llenó la literatura, el pensamiento y los sentimientos de legisladores, gobernantes y otros profesionales de servicios humanos en los años 70, se dudó, del valor del servicio médico. Esto como una

reacción a la complejidad de la tecnología médica y al aumento ascendente de los costos de su uso, igualmente reconocemos, la tendencia a la búsqueda excesiva de lo natural, cada vez que hay un resurgimiento de la tecnología médica. Como la hubo en contra de la pasteurización de la leche, de la clorinación de las aguas y del uso del fluoruro para reducir las caries. Sin embargo, sabemos también que hay prueba definitiva de que el cuidado médico tiene un efecto negativo y estadísticamente significativo en las tasas de mortalidad. Lo que implica que la salud mejora, según el uso del cuidado médico aumenta.

Y aquí le sugerimos a nuestros gobernantes: No caigan en la visión simplista de la dicotomía entre la prevención y servicios médicos. Y le decimos, manejen con extremo cuidado, con delicadeza; la aplicación de incentivos y desincentivos económicos para fomentar una práctica particular de la medicina. Y a nuestros socios le decimos: "Ustedes, si hacen prevención cuando tratan sus pacientes." Cuando usted le indica a su paciente que tuvo un episodio de dolor en el pecho, que baje el consumo de grasas, que deje de tomar y usar cigarrillo, que comience a hacer ejercicios. ¿Está usted previniendo, tratando, o ambas?

A nuestro gobieron y nuestras escuelas de medicina le preguntamos ¿siguen ustedes con la dicotomía de prevención y servicios médicos? Se justifica todavía las clínicas llamadas de "Well Baby". ¿Han integrado ya el currículo de salud pública con los de medicina? ¿Han estudiado el impacto de la sobre oferta de médicos en la calidad de los servicios? ¿Le están dando en sus currículos, en términos de tiempo, la importancia que requieren las eventualidades que están diezmando nuestra juventud, los suicidios, homicidios y accidentes? ¿Le están enseñando a los estudiantes la importancia de los valores humanísticos en la práctica de la medicina moderna? Medicina que esta al presente amenazada por la sobre utilización del criterio de costo en el diseño de los servicios. La medicina que tiene que tolerar que se establezca los DRG's (precios estimados prospectivos) donde se clasifican los pacientes como enfermedades y les fijan precios.

A todos nosotros, médicos y pacientes, políticos y votantes, consumidores de servicios y contribuyentes: se nos debe, a todos, hacer consciente de la vulnerabilidad de la práctica del arte de la medicina, para ser distorsionada, cuando se pone el Costo como criterio principal para determinar los servicios. Ante este iminente peligro para la práctica libre de la medicina y la salud de los pacientes, cobra valor único, la importancia de que nosotros los médicos, mantengamos nuestra posición firme, de excelencia de servicios, ante los administradores que están básicamente dirigidos por la ganancia. Sobre todo debemos exigirle a los gobernantes y legisladores que medien entre estas dos fuerzas y eviten inclinarse excesivamente hacia el costo.

Para hacer claro esta vulnerabilidad paso a un ejemplo: Recientemente, en una "presentación de casos", no de pacientes de un hospital de área, que esta bajo contratos de varias corporaciones, se suscitó la siguiente situación:

Una joven doctora se quejó de que no había podido admitir un paciente grave, al área de intensivo, debido a que dicha área estaba llena. Al discutir las razones se determinó que, las enfermeras de la sala se negaban a manejar algunos casos complicados, por falta de personal. Exigían entonces que, estos casos complicados. según su visión, se mantuviesen en intensivo. Esto provocaba el que se retenían y admitían a intensivo pacientes que usualmente no ameritaban estar en dicha sala. A su vez esto impedía que pacientes graves que requerían ese tratamiento no pudiésen beneficiarse en esa unidad. Con las posibilidades de que se dificultase seriamente su manejo, se complicase su condición y pudieran morir prematuramente. Se trajo el factor de que la situación económica del hospital no era buena, por lo cual no podían de momento aunmentar el personal de enfermería. Sin embargo, la doctora se mantuvo firme. Hizo énfasis en que los médicos no podemos actuar en base a que "La Administración" del hospital no tenga recursos para asignar enfermeras necesitadas y aceptar, el que se admita al área de intensivo pacientes que no ameriten estar ahí. La doctora nos pidió apoyo para no permitir que se cambiase una norma, obviamente sabía, ante una presión indirecta de la administración. El resultado de la posición valiente, honesta y sobre todo reflejo de una práctica excelente de la medicina de la doctora. fortaleció el que se mantuviesen las normas para la utilización adecuada de intensivo. Parece sencillo pero, es complicado, podrían los administradores acusar de irrealista a la doctora pero, ella está manteniendo una posición que nunca debemos ceder los médicos. Es y deber ser siempre, nuestra preocupación única, el cuidado, la salud y la vida de nuestros pacientes por sobre otros intereses.

En la discusión que les acabo de relatar pueden apreciar las serias complicaciones que podrían surgir de estar los médicos en un hospital, tan identificados con la administración, que estén dispuestos a resolver un problema de personal admitiendo inadecuadamente, a pacientes al área de intensivo. Complicaciones como esta seguirán urgiendo siempre que el poder decisional que tenga una corporación con fines pecuniarios, prevalezca o pueda prevalecer sobre las decisiones médicas. Sabemos que este poder se va a multiplicar si los médicos, terminan siendo empleados de estas corporaciones. ¿Dónde va a quedar nuestro paciente? ¿Un objeto más de consumo? ¿Un producto de una corporación gigantesca que tiene sus oficinas en Kalamaozoo, Michigan? o peor, clasificados por los DRG's como enfermedades con un precio fijo, que entre otras cosas pondrán a los hospitales en curso de confrontamientos con los médicos, al estos tratar de mantener su libertad de criterio y decisión. Si todos estamos conscientes en Puerto Rico de como la ganancia distorsiona tanto los servicios públicos... si ya hemos descubierto nosotros mismos, a través del uso de nuestro médico personal, el valor, en términos de garantía de calidad, de que el médico tenga que responder a un paciente, a su paciente. Si todos sabemos del beneficio de que ese paciente le pague directa o indirectamente a su médico, sin otros intereses intermediarios que distorcionen esa relación. Si creemos en estos principios, debemos pedirle a nuestro gobierno que actue con cuidado, con precaución. Que reconozcan la sabiduría detrás del balance de poder en cualquier institución. Los médicos no debemos ceder a nuestra posición de que se tomen las decisiones médicas basadas exclusiva o primordialmente, en la calidad de los servicios que recibe el paciente. Ahora más que nunca, debemos fortalecer nuestros valores, la dedicación a nuestros pacientes. No tratamos enfermedades y si personas, y sus vidas no tienen precio.

Le recordamos a nuestro gobierno que la asociación médica esta comprometida con el desarrollo de alternativas, que bajen el costo de servicios de salud, sin que se distorsionen los criterios primordiales en la toma de decisiones de dichos servicios. Sin que se afecte esa medida única de garantía de calidad, que es la relación médico-paciente. Sin que se le entreguen pacientes y médicos a corporaciones con fines lucrativos. Las implicaciones para la salud del pueblo son muy graves para permitir que situaciones como las que hemos mencionado se generalizen y puedan ocurrir en un futuro inmediato en Puerto Rico. Ante esta situación: ¿Qué le ofrecemos a nuestros socios?

La Asociación Médica de Puerto Rico está ofreciendo adiestramiento a los socios para que mejoren su eficiencia en sus oficinas. Para que consideren otras alternativas de brindar sus servicios y asi mantengan la excelencia de los mismos a la vez de que se tratan de bajar los costos. Necesitamos sin embargo, que el gobierno se una a nosotros en esta tarea. Inclusive, legisle para que promueva mediante incentivos el establecimiento de alternativas que a la vez que se reduzcan costos, mantengan la libre selección y el ejercicio libre de la medicina.

Nuestro objetivo en términos de servicios a nuestros socios es mejorar sobre todo su educación en las áreas de mercadeo, negociación, establecer coaliciones y hacerlos conscientes que estos adiestramientos pueden llevarse a cabo dentro del contexto de nuestros valores, de excelencia de la práctica de la medicina y nuestra dedicación única por nuestros pacientes.

Para poder llevar a cabo un programa intenso de educación a nuestros médicos y de mejoramiento de los mismos como líderes en el campo de la medicina, se requiere, entre otras cosas, una reorganización administrativa de la institución. Estamos ya en el proceso de armonizar la fase administrativa de nuestra asociación con sus objetivos principales y su dedicación a servirle a nuestros socios y por sobre todo a servir a los socios potenciales, asi como a la comunidad en general. Se institucionalizará el taller de liderato médico puertorriqueño este año. Se estimulará a que se celebren talleres similares según las necesidades de los distintos distritos y se tratará de que estos fortalezcan sus recursos administrativos. Se mejorará el asesoramiento técnico en el área de salud a nuestra asociación. Y se hará más efectiva la participación de nuestra Asociación en el establecimiento de política pública del país.

Para facilitar la participación de la clase médica en el establecimiento de política pública del país y que podamos llevar a cabo nuestra Agenda de Salud para Todos, estableceremos este año el foro de las instituciones profesionales de salud de Puerto Rico. Este foro permitirá la participación contínua de las distintas asociaciones de salud en Puerto Rico a través de todo el año. Nuestro punto de partida debe ser el hecho de que el problema de salud es de todos. El objetivo primordial es,

salud para todos. El instrumento básico es, salud, por todos nosotros. Este foro, continuado después de un año de trabajo, culminará con la presentación, de la Agenda de Salud para Todos. Estamos seguros que esta agenda será una aportación única de nuestra asociación en conjunto con todas las asociaciones afiliadas de la salud que culminará en la elaboración de medidas legislativas. Medidas que armonicen la escasez de recursos fiscales del gobierno, con los principios y valores de nuestras instituciones y profesiones de la salud, los cuales pondrán por encima de todos, la necesidad de nuestros pacientes.

Comunidad- ¿Cuál será nuestra aportación hacia la salud de la comunidad?

La asociación médica tiene claro su historia de servicios a nuestra comunidad pero, como los tiempos cambian, cambiarán también nuestros enfoques. Nuestro rol de educación a la comunidad va a ser uno positivo, dirigido en términos generales a lo que es la medicina, sus especialidades, lo que es el médico y las enfermedades. La forma de impedir que nuestros ciudadanos busquen tratamientos para sus enfermedades, fuera del ámbito de la medicina científica, es hacer los servicios accesibles, disponibles, visibles y continuamente ofrecer información sobre la utilidad de los mismos. Hay que hacerle claro a nuestra comunidad que la alta tecnología no esta reñida con unos servicios humanitarios. El uso de medicamentos no quiere decir que los médicos no apoyen el uso de dietas sanas, ejercicios y buenos estilos de vida. Creemos que nuestro mejor amigo es el paciente bien informado. El mejor médico, es el que cuida bien de sus pacientes. Y hoy día, informar es cuidar.

Continuaremos envolviendonos en los temas vitales de salud de nuestra comunidad que por una razón u otra, el gobierno u otras instituciones no asumen el liderato esperando. Ejemplo, todos sabemos que el alcohol es una droga. Todos sabemos que el alcoholismo es uno de los problemas más serios de salud de este pueblo. Todos estamos conscientes que el consumo de alcohol per capita de nuestro país es uno de los más altos del mundo entero. Sabemos que las muertes por accidentes en nuestra carretera, es una de las tres mayores causas de muerte en nuestra juventud. Es una enfermedad fatal y esta intimamente relacionada al consumo del alcohol. Ante todas estas realidades nos preguntamos en la Asociación Médica ¿Cómo es posible, que en nuestra sociedad se promueva por medios de comunicación masiva el consumo de una droga que mata y hace sufrir a miles de puertorriqueños? Hasta ahora la intensión de proteger nuestra juventud ha sido tímida. No podemos ser tímidos con un problema de esta magnitud. Tomaremos iniciativa para que se presente legislación dirigida a que se prohíba el anuncio del consumo de bebidas alcoholicas a través de la televisión. Señores, aquí no hay términos medios. La amenaza es seria y la asociación tiene que tener clara su posición. Igualmente nos dirigiremos a que se suba la edad en la cual se pueda ingerir bebidas en sitios públicos. Es en estos, donde más nuestra juventud bebe sin control y supervisión de sus familiares. No entendemos que podamos comparar el uso de un derecho como es el votar, con el que se permita libre y publicamente, el consumo prematuro de una droga que nos mata, que nos limita, que nos causa profundo dolor a la familia puertorriqueña.

No creemos que cuando esta en juego la vida de jóvenes puertorriqueños se pueda negociar con los que la despachan, ni con los que la producen, ni con los que reciben dineros manchados con la sangre de nuestra juventud. Asi mismo la licencia para guiar automóviles, debe ofrecerse después de una edad en que la mayoría de nuestra juventud ha terminado por lo menos su cuarto años de escuela superior. Todos sabemos el descontrol relativo de los impulsos que tenemos a los 16 y la rápidez con que logramos control de los mismos a los 17 y 18. Promoveremos el que esta edad se suba para que asi estén autorizados a guiar jóvenes, que al tener mayor control de sus impulsos, podrán reducir la posibilidad de hacerse daños a si mismos y a conciudadanos.

Sabemos todos que no hay nada más importante para un país que la salud y la vida de ciudadanos... estamos todos de acuerdo que la protección, la vida y la salud debe ser una misión de todos, pacientes, médicos, administradores y gobernantes. Sin embargo, los conflictos son numerosos. Conflictos entre médicos y hospitales. agencias de seguros y médicos. Gobierno y corporaciones privadas. Los hospitales, muchos de ellos creados por médicos en su deseo de tener un taller de trabajo de excelencia y dedicados al servicio de su pueblo, no quieren que fracasen sus empresas, pero, no a costa de entrar en conflicto directo con los médicos, sin los cuales los hospitales serían meros cascarones de cemento vacios. No quieren el éxito de sus hospitales a costa de tener que manipular las facultades médicas para que se pongan a sus servicios, pues saben el delicado balance entre los criterios administrativos y médicos para poder conservar la excelencia de la práctica de la medicina.

Los seguros prepagados no quieren tener que subir las primas a un nivel que los saque fuera del mercado como institución competitiva. Pero no quieren hacerlo a costa de pagos injustos a los médicos y convertirlos en sus enemigos. No quieren caer en la lucha, donde unos tratan de conseguir alivio del trato percibido como injusto y los otros a generalizar innecesariamente medidas de control estimuladas por la conducta de un grupo mínimo de proveedores que posiblemente, en su deseo de conseguir trato justo, abusan del sistema. Hay muchas formas de ser injustos (o de parecer injustos) y una de ellas es hacer pagar a los muchos por la falta de unos pocos.

El gobierno debe ser fuerza igualadora y garantizar servicios básicos de salud, de calidad, a los médicos indigentes; pero, sin poner tantos controles que caigan en un monopolio de un servicio indispensable como los de energía eléctrica. Monopolios, que en nuestro sistema democrático, al reconocer que controlan un servicio indispensable para el pueblo, crecen sin controles, sin fiscalización adecuada, sin competencia, y terminan deteriorándose y estableciendo PER SE, situaciones de injusticia social. Situaciones que agudizan los conflictos inherentes a nuestro sistema y los hace disponible a ser utilizados por sectores con intereses distintos al bienestar de nuestro pueblo.

Todos queremos conseguir balance para la igualadad con justicia. Necesitamos, sin embargo, ayuda. El gobierno debe fomentar la industria de la salud. Más, fomento en salud no debe ser sinónimo de crecimiento y si de diversificación, de creatividad. De establecimiento

de sistemas que controlen costos con un mínimo de impacto negativo en la relación médico paciente y en los procesos de dicisiones médicas. Esto debería ser un rol de fomento industrial u otra agencia que no entre en conflicto por ser un proveedor de servicios de salud. En este tipo de servicios creativos, si vemos un rol importante para el sector privado. Esperamos que el foro de organizaciones de salud en su agenda de salud para todos nos pueda presentar alternativas viables de implementación, de la idea del fomento de la industria de salud para todos.

Hay mucho trabajo por hacer. La tendencia a caer en soluciones simplistas es grande. Esperamos poder contribuir como siempre lo hemos hecho. Ayudaremos al manejo de esta nueva situación en salud sin que terminemos con un pueblo con menos libertad, con una profesión que deje de ser la práctica de un arte para ser solo eficiencia y efectividad.

Detrás de todo lo que hemos dicho están los principios de libertad y los peligros de la falta de la misma: la Esclavitud.

Deseo terminar este mensaje con varios pensamientos sobre uno de los valores que más apreciamos: la Libertad.

Es más fácil ser esclavo, que libre ser.
Pero... La Esclavitud hace hombres débiles
Que fácilmente dejan de ser,
Para convertirse en manadas
que luchan sin descansar
Hasta dejar de ver
Lo que más los amenaza
El último hombre libre... pasar.

Es más difícil ser libre, que esclavo ser Pero... La Libertad hace hombres fuertes Que piensen, sienten y viven, Del solo hecho de ser. Y su motivo final, Es a otros enseñar La difícil y a veces imposible tarea De luchar sin descanso Para poder siempre decir. Soy yo y somos nosotros y seremos fuertes Muy fuertes nosotros. Porque tú eres tú Ella es élla Y él es él.

Los médicos somos privilegiados, pues practicamos la última profesión libre en el campo de la salud. Dios quiera, que podamos conservarla asi por el bien de nuestro sistema de vida, de nuestro pueblo y sobre todo por el bien de nuestros pacientes.

Biografía del Doctor José A. Nuñez López

I presidente de la Asociación Médica de Puerto Rico. doctor José A. Nuñez López, nació en Caguas, Puerto Rico, el 23 de septiembre de 1933. Fue graduado Magna Cum Laude de la Universidad de Puerto Rico en el 1953 y de la Escuela de Medicina en el 1958. Hizo su internado de medicina en el Hospital de Distrito de Bayamón y la Residencia de psiquiatría en el Centro de Entrenamiento e Investigación Psiquiátrica de la Escuela de Medicina de la Universidad de Puerto Rico del 1959 al 1962. Es miembro de la Asociación Médica de Puerto Rico desde el 13 de enero de 1962 cuando siendo residente de tercer año solicitó y fue aceptado como miembro afiliado de nuestra Asociación. Para mayo de 1962 fue aceptado también como miembro asociado de la Asociación Psiquiátrica Americana.

Fue iniciador y primer director del Centro de Tratamiento Intensivo del Hospital de Psiquiatría de Río Piedras en 1963, que sentó las bases para el desarrollo de los centros de salud mental de todo Puerto Rico. Después de contribuir a que dicho centro se utilizara para el programa de adiestramiento de la residencia de Psiquiatría del Recinto de Ciencia Médica, fue nombrado Director y Superintendente Auxiliar de dicho hospital. Al realizar las limitaciones que el sistema de una institucional total tenía para brindar servicios a los pacientes mentales, decidió solicitar ser transferido a Caguas, después de ser el autor de la propuesta federal para desarrollar el Centro de Salud Mental de dicha comunidad.

Fue el primer director y fundador del primer Centro de Salud Mental de Puerto Rico que brindó cinco servicios básicos a la comunidad: hospitalización, hospitalización parcial, tratamiento ambulatorio, servicios de emergencia y educación en consultoría. Fue nombrado Secretario Auxiliar de Salud Mental en el 1973. Durante tres años aceleró en forma significativa el desarrollo de los centros de salud mental. Al terminar su incumbencia habían trece centros de salud mental funcionando. Recibió un reconocimiento del Instituto Nacional de Salud Mental. siendo nombrado consultor de la Región II.

Entre los nombramientos académicos que obtuvo del 1962 al 1982 se encuentra el de Profesor Auxiliar de Psiquiatría Clínica en la Escuela de Medicina de la Universidad de Puerto Rico, Profesor Auxiliar y Director del Departamento de Servicios Sociales de la Escuela de Salud Pública y Profesor Auxiliar del Departamento de Medicina de la Escuela de Medicina de la Universidad de Puerto Rico. Además, trabajó como entrenador del aboratorio de conducta humana del Centro Interamericano de la Universidad de Loyola en los veranos 1967 y 1968. Fue miembro por cinco años del Foro de Educadores en Psiquiatría a la Comunidad, grupo de la Universidad de Pittsburg, dirigido por el Dr. Gerald Kaplan.

El Dr. Nuñez López ha ocupado puestos en múltiples instituciones puertorriqueñas, como miembro de la primera Junta de Directores del Centro Médico de Puerto Rico, miembro de la Comisión del Niño y la Comisión de Salud Mental. Ha ofrecido su asesoramiento a los cuerpos legislativos, a agencias de la comunidad, a gobiernos municipales e instituciones voluntarias. Su interés en la labor cívica se refleja en su experiencia al organizar un grupo de dos equipos de profesionales de salud voluntarios que por dos semanas brindaron servicios a las áreas rurales de Don Gregorio y Pizarrete en la República Dominicana en Baní en septiembre de 1979, después del desastre causado por los huracanes David v Federico.

El Dr. Núñez López ha sido distinguido al ser nombrado Fellow de la Sociedad Real de Salud y Fellow de la Asociación Psiquiátrica Americana y recibió el premio presidencial de la Sección de Psiquiatría, Neurología y Neurocirugía de la Asociación Médica de Puerto Rico por su liderato y contribución a la medicina.

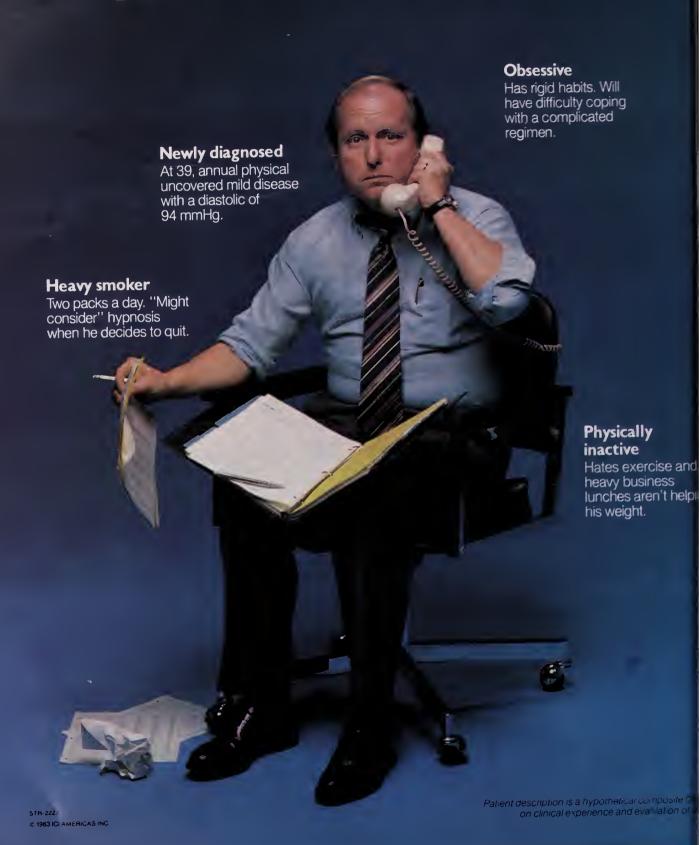
Fue presidente de la Asociación de Salud Pública de Puerto Rico en el 1979, año en el cual también presidió el Distrito Central de la Asociación Médica de Puerto Rico. En el 1980 fue electo Vicepresidente de la Asociación Médica de Puerto Rico. En el 1981 presidió el Consejo de Medicina de Gobierno y en el 1982 presidió nuestra Cámara de Delegados.

Dr. Nuñez López es autor de numerosos artículos de prensa. Ha sido colaborador en el Boletín de la Asociación Médica de Puerto Rico, el cual ha publicado artículos desde el 1962. Bajo su iniciativa y asesoramiento continuo se grabó la cinta videomagnetofónica Violencia en Puerto Rico en 1975 y fue co-autor de libros para el pueblo en el 1976. Tres libros que llevan a la comunidad puertorriqueña en forma clara y sencilla los principios fundamentales para preservar la salud mental.

Al presente, Dr. Núñez López es catedrático Auxiliar del Departamento de Medicina de la Escuela de Medicina de la Universidad de Puerto Rico, ofreciendo sus servicios en la Residencia de Medicina Interna General en el Hospital de Carolina y el Centro de Salud de Canóvanas.

A través de todos estos años el Dr. Núñez López ha sido entusiasta de viajar a través del mundo y ha podido estudiar por contacto directo sistemas de salud de países diversos como Estados Unidos, México, Venezuela, Cuba, algunos de los países de Europa y Rusia. Esta exposición le ha dado una visión amplia de la problemática de salud que junto a haber podido ocupar posiciones de alta responsabilidad en los niveles terciarios, secundarios y primarios, lo convierten en un recurso de gran utilidad para nuestra Asociación.

What can you do for hypertensives like Paul H?



Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Paul H represents 2,514 men under 40 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Paul H's age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Reasons for this are not fully understood, but smoking has been implicated—especially in males like Paul H. TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Paul H...and virtually all your hypertensive patients

TENORMIN® (atendal)





For Paul H... and virtually all your hypertensive patients

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-{2'-hydroxy-3'-{(1-methylethyl) amino] propoxy}- Atenolol (free base) has a molecular weight of 266 It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37. C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension It may be used alone or concomitantly with other antihypertensive agents, particularly with a thisardia-type diuratic.

sion it may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than tirst degree, cardiogenic shock, and overt cardiact failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of turther depressing myocardial contractility and precipitating more severe failure. In hyperensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure; patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn. Ischemic Heart Diseases: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur. Proceedings of the patient should be carefully observed and remaining and processes: Patients with processaries of the reinstated if withdrawal symptoms occur. Processaries are supported to a minimum. TENORMIN should be reinstated if withdrawal symp

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It freatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and frichforcethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agoinsts and its effects on the heart can be reversed by administration of such agents (e.g. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (e.g. profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask fachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyrodism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (e.g. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

of clondine

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times. The maximum recommended by impacting the production of the produ

the maximum recommended human dose) was unaffected by atenolol admini

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenoiol (starting at 15 mg/kg/ day or 75 times the maximum recommended human dose) and increased incidence of afrial degeneration of hearts of male rats at 300 mg but not 150 mg atenoiol/kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo /fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12 5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women TENORMIN should be used during pregnancy only it the potential benefit justifies the

potential risk to the fetus

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

APPENDIANCE AND TENDERS AND TE

is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: tirst from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects).

from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), stight-headedness (1%-0%), tiredness (0.6%-0.5%), stight-headedness (1%-0%), deression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), tatique (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-19%)

RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored tollowing cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress
Central Nervous Syslem: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics
Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis
Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.
Miscellaneous: The oculomicocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practoloc reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with over dosage of a beta-advenergic blocking agent are bradycardia, congestive heart failure, hypotension broad to accompany and this polynomia.

bronchospasm, and hypoglycemia In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted

Brandycardia: Atropne or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker

Congestive Heart Failure: Conventional therapy

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or no

epinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to durette therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit

TENORMIN may be used alone or concomitantly with other antihypertensive agents including

TENORMIN may be used aone or concominantly with other antihypertensive agents including thirazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1 73 m²); therefore, the tollowing maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min 173 m²)	Atenolol Elimination Half-lite (hrs)	Maximum Dosag
15-35	16-27	50 mg daily

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets wistuant embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuar embossed on one side and NDC No 101 embossed on the other side are supplied in bottles of 1 tablets and unit-dose packages of 100 tablets.

Protect from heat light and most time Store unit-dose and calendar packages at controlled to

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled ro

Reterences: 1. Data on file, Stuart Pharmaceuticals 2. Herman RL, Lamdin E, Fischetti JL, Ko F Postmarketing evaluation of atenolol (Tenormin*) A new cardioselective beta blocker *Curr The, Res* 1983, 33(1) 165-171 3. Townley RG. The effect of beta-adrenergic blockade on respiratory function *Primary Cardiol* 1980, 6(suppl 1) 38-46 4. Burrows B. An overview of obstructive lung diseases. *Med Clin North Am* 1981, 65 455-471 5. Zacharias FJ. Companson of the side effects different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980, 6(suppl 1) 86-89.



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IPPB Trial Group. IPPB in COPD. Chest 1984; 86:341-342

El tratamiento con aparatos de presión intermitente positiva (IPPB) se ha estado usando ampliamente, pero no había un estudio en grande escala que comprobara su eficacia. El "National Heart, Lung and Blood Institute" auspició dicho estudio. Cinco importantes centros clínicos participaron. Se incluyeron más de mil casos de enfermedad crónica obstructiva pulmonar tratados ambulatoriamente. Se asignaron a terapéutica inhalatoria con broncodilatadores (por métodos aleatorios) a IPPB o al mismo medicamento administrado por nebulizador impulsado por aire comprimido. El estudio duró tres años. No hubo diferencia entre los dos grupos en lo concerniente a la evolución clínica, mortalidad, número de hospitalizaciones, calidad de vida y función pulmonar. Se concluye que en estos casos el tratamiento con IPPB no está justificado.

José E. Sifontes, MD, FAAP

WHEN TO PERFORM BIOPSIES OF ENLARGED PERIPHERAL LYMPH NODES IN YOUNG PATIENTS. Slap GB, Brooks JSP, Schwartz JS. JAMA 1984; 252:1321-1326

Los autores revisaron los expedientes de 123 personas de 9 a 25 años de edad a quienes se les habían practicado biopsias de nódulos linfáticos superficiales; revisaron la histopatología y la relación con el cuadro clínico y el diagnóstico final. En 42% se encontraron lesiones granulomatosas o malignas que confirmaban la necesidad de la biopsia. En estos casos apuntaban hacia la indicación para biopsia la radiografía de torax anormal y el tamaño del nódulo de más de 2cm o si éste provenía de la región supraclavicular o del músculo escaleno. Los que tenían síntomas de las vías respiratorias altas solían tener lesiones benignas. Se recomienda el seguimiento de estos casos a largo plazo y si es necesario, repetir la biopsia.

José E. Sifontes, MD, FAAP

CHRONIC PERCUTANEOUS PERICARDIAL DRAINAGE WITH MODIFIED PIGTAIL CATHETERS IN CHILDREN Lock JE, Bass JL, Kulik TJ, el al. Am J Cardiol 1984; 53:1179-1182

En el diagnóstico y manejo de la acumulación de líquido en el espacio pericárdico contamos con la punción con aguja (casi siempre se requieren varias punciones), el drenaje quirúrgico y el drenaje con tubos pericárdicos. Estos últimos frecuentemente se obstruyen ya bien sea por coágulos o por efusiones viscosas impidiendo el buen resultado terapéutico.

En vista de ello, los autores, del Departamento de Pediatría del Hospital de la Universidad de Minnesota realizaron un estudio para determinar el cateter óptimo para el drenaje por vía percutánea de efusiones pericárdicas con tendencia recidivante. Ellos utilizaron un cateter "pigtail" tamaño 8.3F al cual le agrandaron los orificios hasta 0.055".

Con punción en el área xifoidea utilizando una aguja 18 de 7cm y "rastreo" electrocardiográfico se penetró la cavidad pericárdica, se introdujo un "guidewire" y luego de confirmar su posición fluoroscópicamente se colocó el cateter en la región pericárdica posterior. Se adaptó el cateter a una succión continua de 20cm H₂0 y se obtuvo el drenaje eficaz y prolongado deseado.

Los autores creen que este procedimiento es el método de elección para el drenaje pericárdico crónico, reservando el drenaje pericárdico quirúrgico para aquellos casos en que el cateter no sea efectivo.

Rafael Villavicencio, MD, FACC

LA EVALUACION DE HIDRONEFROSIS FETAL EN EL RECIEN NACIDO: TIEMPO OPTIMO PARA REALIZAR LA SONOGRAFIA DE SEGUIMIENTO: Laing FC, Radiology Journal 1984; 152:423

Aunque la hidronefrosis fetal intrauterina puede ser detectada fácilmente por ultrasonido, el estudio de seguimiento del primer día de vida extrauterina del neonato puede mostrar unos riñones que aparezcan falsamente normales. Los autores de este artículo presentan 3 infan-

tes en los cuales el estudio inicial fue falsamente negativo y en los que el estudio de seguimiento confirmó la presencia de obstrucción del tracto urinario alto. Se postula que la apariencia normal de los riñones en el primer día de vida extrauterina probablemente se debió al relativo estado de deshidratación durante las 24 primeras horas de vida y la filtración glomerular disminuída de esas primeras horas. Se recomienda por tanto que el sonograma inicial post partum sea realizado varios días luego del nacimiento del bebé en el cual se haya hecho el diagnóstico de hidronefrosis intrauterinamente.

Bernardo Marqués, MD

PATIENT SELECTION AND SURVIVAL AFTER PERITONEOVENOUS SHUNTING FOR NONMALIGNANT ASCITES. Smith RE, Nostrant TS, Eckhauser FE, et al. Amer J Gastro 1984; 79:659-662

Los autores reportan su experiencia con 30 pacientes a quienes se les puso un puente peritoneo-venoso para tratamiento de ascitis. Catorce pacientes habían tenido ascitis refractoria al tratamiento médico (AR), 10 tenían ascitis y el síndrome hepatorenal (SHR), y seis tenían ascitis recurrente, pero no refractoria (NR). La etiología de ascitis era cirrosis por alcohol en 25, Budd-Chiari en 3, cirrosis postneurótica en 1 y cirrosis criptogénica en 1. Algunos datos del estudio son los siguientes: 1) la sobrevida después de la operación fue de 767 ± 214 días en NR, 256 ± 148 días en AR, y 28 ± 5 días en SHR. 2) El 70% de los pacientes con SHR murieron durante la hospitalización y ninguno sobrevivió un año; 4 de 6 pacientes con NR y 2 de 14 con AR sobrevivieron un año. 3) Complicaciones graves en el periódo postoperatorio ocurrieron en el 47% de los pacientes. Coagulación intravacular diseminada con manifestaciones clínicas se encontró en 23% de los pacientes, sepsis en 13%, peritonitis en 7%, fallo congestivo cardíaco en 10% sangramiento gastrointestinal en 10%, y otras complicaciones como pulmonía, ARDS, encefalopatía en como 3% de los pacientes. 4) Veinte y dos de 39 puentes quirúrgicos funcionaron mal (19 de 26 puentes tipo Le Veen, 3 de 13 tipo Denver; p 0.001). Los autores comentan que hasta el momento no hay un buen estudio prospectivo reportado comparando la eficacia y seguridad de esta operación con un grupo similar tratado médicamente.

Angel Olazabal, MD, FACP

ANTIBIOTIC PROPHYLAXIS IN PATIENTS WITH ACUTE LEUKEMIA. Estey E, et al. Arch Intern Med 1984; 144:1562

Las infecciones permanecen siendo la causa principal de muerte en pacientes con leucemia aguda y es especialmente común durante los períodos en donde el paciente tiene granulocitopenia severa. Inicialmente los bacilos gram-negativos eran los patógenos más frecuentes, pero los coco gram-positivos también han surgidos como causas frecuentes cuando se han utilizado sondas endovenosa centrales largas. El uso de agentes antibacterianos de amplio espectro ha aumentado la incidencia de infección por hongos. Los antibióticos orales no absorbibles combinados con el cuarto de flujo laminar se han utilizado para reducir la frecuencia de infección, pero su efectividad en un hospital común y corriente no se ha demostrado consistentemente. En años recientes trimetropin-sulfametoxazole se ha utilizado para profilaxis en contra de infección. A pesar de la habilidad de este medicamento, de mantener lo que conocemos como el factor resistente a colonización dentro del intestino, las infecciones por organismos resistentes a este medicamento han surgido. Por esto, los agentes anti-hongo se han añadido al régimen de profilaxis.

Estey y asociados estudiaron 147 pacientes con leucemia aguda que estaban recibiendo tratamiento de inducción remisión. Los pacientes fueron randomizados a recibir lo siguiente: Ningún profilaxis (38 pacientes): trimetropin-sulfametoxaxole (1 tableta de doble concentración, dos veces al día) (35); ketoconazole (200 mg dos veces por día) (32); y una combinación de trimetropinsulfametoxazole y ketoconazole (45 pacientes) en las dosis mencionadas anteriormente. El porciento de los pacientes en donde se desarrolló infección, fue más alto en los que no recibieron profilaxis o en los que recibieron ketoconazole; fue intermedio en los que recibieron trimetroprin-sulfametoxazole y el más bajo en donde recibieron terapia combinada. La infección más frecuente en todos los grupos fue pulmonía o septicemia. Las infecciones bacterianas fueron más frecuentes y más severas que las infecciones por hongo: 89 infecciones bacterianas ocurrieron en 51 pacientes, mientras que 31 infecciones por hongo ocurrieron en 26 pacientes. Los cocos gram positivos fueron responsables por 45 infecciones bacterianas y los bacilos gram-negativos por 36. Trimetroprinsulfametoxazole fue igualmente efectivo en contra de ambos grupos de micro-organismos. Trimetropin-sulfametoxazole aparentemente logra disminuir la severidad de infección por Pseudomonas. A pesar de que trimetropin-sulfametoxazole disminuía las infecciones bacterianas, o la morbilidad de las infecciones bacterianas y que el añadir ketoconazole reducía la morbilidad de infección por hongo, la tasa de mortalidad básica asociada con el proceso de inducción remisiones en pacientes con leucemia a través de quimoterapia que produce granocitopenia, no cambió. La frecuencia de remisiones completas con o sin profilaxis no fue diferente en ninguna de las combinaciones.

COMENTARIOS: Hastas el momento no se ha diseñado una manera perfecta para prevenir infecciones de pacientes con leucemia aguda, que por necesidad deben convertirse en granocitopénico de tal manera que se pueda lograr una remisión completa de su enfermedad. Los antibióticos absorbibles a pesar de que no son perfectos, aparentan disminuir la incidencia de sepsis o pulmonía sin destruir todas las defensas que presentan la flora del propio paciente. La mejor combinación sugerida es trimetroprin-sulfametoxazole y ketoconazole. La combinación de trimetropin-sulfametoxazole es relativamente no tóxica, a no ser por reacciones alérgicas de

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estos agentes y la posibilidad de que puedan deprimir la médula osea. Los efectos más importantes de ketoconazole es enterocolitis. El médico debe reconocer que no se ha demostrado que ketoconazole sea efectivo en el tratamiento de infecciones en donde la vida de paciente pueda estar en juego. Amfotericina B es el agente que se utiliza como primera línea en estas infecciones.

El uso de antibióticos profilácticos debe diferenciarse del uso de tratamiento directo cuando se sospecha sepsis en el paciente granulocitopénico. El régimen reportado en este artículo es un régimen inadecuado para el tratamiento de sepsis o pulmonía en este tipo de paciente.

Es indispensable utilizar antibióticos por vías endovenosa de amplio-espectro que usualmente es la combinación de una penicilina con actividad antipseudomonica y/o una penicilina con actividad anti-estafilococcica más un aminoglucósido para cubrir los patógenos gramnegativos. Solamente ocasionalmente, podría considerarse una cefalosporina de tercera generación en adición o en combinación con otro agente. Amfotericina B puede añadirse a este régimen si la fiebre u otro signo de infección no se define en 4 a 7 días.

C. Ramírez-Ronda, MD, FACP

CAMPYLOBACTER IDENTIFICATION IN MALE HOMOSEXUALS. Quinn TC, et al. Ann Intern Med 1984: 101:187

El género Campylobacter incluye varias especies de bacilos Gram-Negativos que cada vez se reconocen como una causa más frecuente de infección humana y se ha observado un aumento en la comunidad homosexual. Produce un síndrome diarreico que varía desde una enfermedad leve a una enfermedad con manifestaciones hemorrágicas. El contacto oral-anal entre los homosexuales; facilita la transmisión de infecciones intestinales con otros patógenos e infecciones con los especies de Campylobacter y organismos parecidos. La cantidad de inóculo necesario para transmisión es baja, por lo tanto se facilita el modo de transmisión fecal-oral.

Quinn y sus colaboradores, estudiaron 158 varones homosexuales o bisexuales sintomáticos y 75 varones homosexuales o bisexuales, 75 varones heterosexuales además de 75 mujeres heterosexuales como controles asintomáticos. C. jejuni se aisló de 10 de los estudiados sintomáticos y 2 de los varones homosexuales asintomáticos; los organismos parecidos a Campylobacter fueron identificados en 26 homosexuales varones sintomáticos y 6 homosexuales varones asintomáticos. No se identificaron organismos en los 150 varones y mujeres heterosexuales. La presencia de síntomas de infección incluyen varias combinaciones de diarrea, cólicos abdominales, tenesmus, hematochezia, descarga anal, dolor anal y fiebre. Evaluaciones previas de varones homosexuales que se quejan de síntomas gastrointestinales fallaron en recobrar el organismo cuasante.

Este estudio sugiere que los organismos parecidos a *Campylobacter y C. jejuni* pueden ser una causa identificable de infección de los pacientes que tienen proctoco-

litis en esta población. Como estos organismos son difíciles de crecer, los autores sugieren que se siembren directamente los isopos rectales en los medios de cultivos. El medio de cultivo utilizado no tenía Cefalotina y los cultivos se incubaron a $37^{o}C$ que ha sido recomendado para recobrar C. jejuni. Los organismos como *Campylobacter* crecen más lentamente; consecuentemente, los cultivos descartados de 48 a 72 horas, pueden interpretarse como falso-negativos.

COMENTARIOS: La enfermedad por *Campylobacter* puede verse en el síndrome que se ve en pacientes homosexuales y que envuelve la presencia de diarrea sanguinolenta, fiebre, y a veces retortijones abdominales severos. Es importante recobrar este organismo porque es una enfermedad tratable y el fallo en recobrar este organismo puede causar transmisión en otros pacientes. El clínico debe de notificar al laboratorio que quiere recobrar Campylobacter, de tal manera que se use medios de cultivos selectivos a temperaturas específicas de incubación. La misma regla aplica para cualquier bacteria que requiera cultivos especiales y que no se recobre normalmente en situaciones clínicas. Inoculando al huésped a través del canal-anal una respuesta inmunológica única se desarrolla debido a que el antígeno en el intestino se integra por los mecanismos de defensa inmune del huésped en una manera diferente como sería cuando se introduce una antígeno a través de la cavidad oral o a través del pulmón. Parte de la inmunidad deprimida que se ve en pacientes puede ser modificada aun más por este patrón de contacto del antígeno por vía anal. El tratamiento de primera línea para Campylobacter es eritromicina. Al igual que en otras causas de diarrea no está claro si este tipo de tratamiento es de algún beneficio. El tratamiento puede impedir el sanamiento y prevenir que se desarrolle una respuesta inmune completa a éste organismo. Cuando hay una infección severa el tratamiento está indicado y a veces puede ser que se salve la vida del paciente.

C. Ramírez-Ronda, MD, FACP

THE DROOPY SHOULDER SYNDROME. Swift TR, Nichols FT. Neurology 1984; 34:212-215

Patients with thoracic-outlet syndrome have: (1) low-set, "droopy" shoulders and long swan neck, (2) pain in the neck, shoulder, chest, arms, or hands, (3) aggravation of symptoms by downward traction and relief by propping up the arms, (4) occurrence in women, (5) absence of abnormal vascular, neurologic, and electrical findings, (6) a Tinel's sign over the brachial plexus, and (7) T-2 vertebra visible above the shoulders on lateral cervical spine films. In our experience, droopy shoulder syndrome has accounted for most cases of thoracic-outlet syndrome. Recognition of this syndrome should lead to better treatment programs and possibly eliminate unnecessary surgery.



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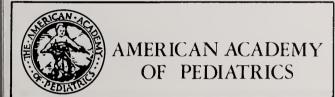




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ACADEMY PERTUSSIS TASK FORCE MEETS

A high-level task force convened by the Academy has identified five goals aimed at preventing a pertussis public health crisis.

At its early August meeting, the Pertussis Task Force agreed that maintaining a high level of immunization, educating physicians on possible contraindications to additional doses of the vaccine and educating the public to both the risks and benefits of immunization would help avert a crisis. Participants also agreed that a compensation system to help parents whose children react adversely to the vaccine, such as the one outlined by the National Childhood Vaccine Injury Act pending in Congress, also is necessary. A safer, more effective vaccine also should be developed, the task force said.

Formed by the AAP's Executive Board last spring, the task force's work took on extra urgency after Wyeth Laboratories, one of the three U.S. companies manufacturing the pertussis vaccine, announced June 13 that it was halting production.

Lederle Laboratories, one of the two remaining vaccine manufactures, said after the Wyeth announcement that it was increasing its production of the pertussis antigen. The company added that it was forced to increase the price of a standard 15-dose vial to \$42. That is the same amount charged by Connaught Laboratories, the other remaining U.S. manufacturer.

Philip Brunell, M.D., chairman of the AAP's Committee on Infectious Disease pointed out that children with certain pre-existing conditions may not be candidates for the vaccine.

"Children who have personal histories of convulsion or who have certain neurologic conditions that predispose them to convulsion should have their immunizations deferred," ha said. He added that children who have any of the following reactions after receiving a pertussiscontaining vaccine should not receive additional doses: severe neurologic reaction; persistent screaming for three hours or more; excessive somnolence, temperature of 105 degrees Fahrenheit or more; or convulsions within 48 hours of immunization.

News & Comment, AAP, 1984; 35(9):1-2

MIDDLE EAR DISEASE AND LANGUAGE DEVELOPMENT

There is growing evidence demonstrating a correlation between middle ear disease with hearing impairment and delays in the development of speech, language and congnitive skills. Middle ear disease may be so subtle that a full evaluation for this condition should combine pneumatic otoscopy, and possibly tympanometry, with a direct view of the tympanic membrane. When a child has frequently recurring acute otitis media and/or middle ear effusion persisting for longer than three months, hearing should be assessed and the development of communicative skills must be monitored.

News and Comments AAP, 35:(9):9, 1984

HONEY INDUSTRY GROUP RENEWS WARNING ON BOTULISM

A recent outbreak of infant botulism has reaffirmed previous warnings that infants should not be fed honey, according to the Honey Industry Council of America, Inc.

Widespread bacteria, C. botulinum are carried by dust and commonly found on fresh fruits, vegetables and other agricultural products, including honey. Older children and adults can ingest the bacteria's inactive spores without harm, which is quite different from ingesting active, preformed toxin.

The Academy's statement recognized that "many children with the illness had no history of honey ingestion," but said "it is probably prudent" to follow the U.S. Centers for Disease Control's suggestion that honey not be fed to infants younger than six months, the age group at highest risk.

Since the spores are so widespread, the Honey Industry Council says that it is likely that most if not all infants are exposed to *C. botulinum* spores, but that only a fraction become infected.

The organization its warning that honey should not be fed to infants, but extended its warning to include infants up to one year of age.

News & Comment, AAP. 1984; 35(9):9

BURN PREVENTION WORKS WHEN PARENTS TAUGHT BASICS

Prevention education does its job, according to a new study. A series of classes proved to be an adequate incentive to convince parents to follow burn prevention procedures such as lowering hot water heater settings at home and increasing fire safety knowledge, says a study in the November issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP).

The study, conducted at the University of Kansas Medical Center in Kansas City, tested fifty-eight couples, similar in age and education and members of an HMO in a large metropolitan city, who volunteered for well-child care classes teaching home safety procedures. The control group was given information on nutrition, car and home safety and child development during seven 90-minute sessions. The experimental group was given the same material plus additional information on hot water heater settings and smoke detectors, for nine 90-minute classes.

In follow-up visits, 65 percent of the parents in the experimental group had lowered their hot water heater settings to 130 degress F. or below, while all of the couples int he control group had settings higher than 130 degrees F. The experimental group also had significantly higher scores on a written fire safety knowledge test.

Past studies have shown that when health education is effective it is because one behavior is targeted. This study led the researchers to speculate that parents may have felt they "made their baby or child safer" simply by lowering the temperature of their hot water heaters.

The AAP's Injury Prevention Program (TIPP) recommends a safe hot water heater setting between 120 and 130 degrees F to protect children from scalding. That is crucial for children because burns are the leading cause of death in the home for children ages one to four. Burn injuries rank only second to auto accidents as the major cause of accidental death in all children (birth to 15 years of age).

The Academy recommends that if a child does get burned, put the affected area in cold water immediately. Then cover the burn loosely with a bandage or clean cloth. Call your pediatrician for any severe burn your child might receive.

The study concludes that pediatricians can have a significant impact in working with parents to implement burn safety procedures in the home. The AAP recommends that pediatricians include home safety information as a routine part of a well-child care.

AMERICAN COLLEGE OF PHYSICIANS



CEAP EVALUATES GLYCOSYLATED HEMOGLOBIN ASSAYS FOR DIABETES MANAGEMENT, DIAGNOSIS

Recommendations on the use of glycosylated hemoglobin assays in the management and diagnosis of diabetes mellitus have been published by the American College of Physicians (ACP) in the November issue of *Annals of Internal Medicine*. The statement is issued as part of the College's Clinical Efficacy Assessment Project (CEAP), by which the ACP evaluates the safety, efficacy and cost of medical tests, procedures and therapies and makes recommendations on their appropriate uses.

Diabetes mellitus, a disorder in which the body fails to produce insulin or does not use it properly to control the level of sugar in the blood, affects approximately 11 million people in the United States.

Control of the diabetic patient's blood glucose levels may be obtained with a variety of treatments, which usually involve a combination of multiple daily insulin injections and intensive blood glucose measurement. The discovery tha blood levels of glycosylated hemoglobin may be elevated up to three times normal in people with diabetes led to the use of glycosylated hemoglobin measurement in managing and diagnosing the disease.

Glycosylated hemoglobins make up 5% to 8% of hemoglobin A (HbA), which constitutes about 90% of all hemoglobin found in the average normal adult's red blood cells. The levels of two groups of the glycosylated hemoglobins, HbA₁c and pre-HbA₁c, as well as the total amount of HbA, are elevated in persons with diabetes.

"Glycosolated hemoglobin assays may provide useful information regarding the diagnosis and management of diabetes mellitus in selected patients," the ACP says. The main risk involved with the procedure is when faulty or misinterpreted test results are used as a basis for therapy. Levels of labile components may change within hours to weeks in response to acute changes in blood glucose levels, so only assays that remove labile components or do not measure them should be used.

The ACP notes the various different laboratory methods used to measure glycosylated hemoglobin: chromatography, electrophoresis and colorimetric methods. When care is taken with specimen handling and with the analytic technique, each method is capable of providing accurate, useful data. The College warns, however, that each method has its own limitation. For a meaningful interpretation of the results, the clinician must understand the analytic method used along with its limitations, the reference values used and HbA components measured.

The procedure's usefulness is hindered by the lack of a well accepted standard method of high precision and replicability, according to the CEAP study. Because measured levels of glycosylated hemoglobin are significantly affected by even minor methodologic differences, the ACP warns that comparing values obtained from different laboratories, even when the same method is used, is "fraught with hazard."

As a test to diagnose diabetes mellitus, glycosylated hemoglobin has low sensitivity--directly related to the quality of the assay--but is highly specific (above-normal levels almost certainly indicate diabetes). Borderline results should be interpreted cautiously because of the lack of reliable reference levels, the ACP cautions. The predictive value of glycosylated hemoglobin levels as an indicator of the subsequent development of diabetes is not known, nor is the significance of elevated levels in a person who lacks other symptoms of diabetes.

Assessment of the degree of blood glucose control in

many diabetic patients is enhanced by the measurement of two groups of glycosylated hemoglobins, HbA_1 and HbA_{1c} , says the ACP. The College indicates that these assays are particularly advantageous when patients are performing urine testing in the face of unknown renal thresholds; when patients do not comply with home glucose or urine glucose testing; when patients are suspected are suspected of falsifying home blood glucose monitoring records; and when patients are suspected of poor compliance with therapy until the days immediately preceding a physician visit.

In the pregnant diabetic patient, glycosylated hemoglobin measurements are useful to establish a baseline degree of blood glucose control, according to the CEAP statement. They also are recommended as an adjunctive measure to check the validity of the patient's home measurements when tight control is desired, as is the case

with pregnant diabetic patients.

The College warns that glycosylated hemoglobin assays are not useful in acute care management decisions of unstable diabetes. They can, however, provide an objetive index of glucose control for clinical trials evaluating alternative modes of therapy, and may give information over time on the relation of blood glucose control to diabetic complications.



ALCOHOL AND TRAUMA

Alcohol consumption is an underlying but often overlooked risk factor for many injuries, including vehicular accidents, falls, drowings, homicides, suicides, and burns, according to a collective review appearing in the November issue of *Annals of Emergency Medicine*.

Injuries, both intentional and unintentional, now rank as the fourth leading cause of death in the United States, outranked only by heart diseases, cancer, and stroke. Yet when viewed in terms of unnecessary loss of life, accidental injuries must be ranked first, for accident victims are usually much younger than persons dying from other more frequent causes.

Vehicular Accidents

The article notes results of numerous studies of fatally injured drivers, showing approximately 40% to 50% have blood alcohol levels of 0.10% or higher. These figures contrast sharply with noninjured drivers in automobile accidents, with only 2% to 3% of this group having blood alcohol levels this high. Because alcohol is a known central nervous system depressant, the frequency of its use in these fatally injured drivers and its relative absence in the control group of drivers strongly suggests that drinking greatly increases the risk of a fatal automobile accident. The strength of this association is even greater

for drivers killed in single-vehicle crashes - in this group almost two-thirds have blood alcohol levels indicating legal intoxication.

According to Albert B. Lowenfels, MD, author of the study, young drivers constitute a high-risk group especially prone to fatal automobile accidents. Although 16-to 24-year-old drivers make up only 17% of the US population, this age group was involved in 45% of all fatal highway accidents in 1981. Alcohol played a prominent role in these deaths. Currently it appears that injuries from alcohol-related motor vehicle crashes are the leading cause of death in the 16- to 24-year-old group.

Pedestrian Injuries

Studies of automobile-pedestrian accidents show that the pedestrian has often been drinking prior to the accident.

"The intoxicated pedestrian has at least three to four times greater likelihood of being struck by an automobile than does a sober pedestrian," reports Dr. Lowenfels.

Falls

The article states that an intoxicated person is more likely to fall and sustain a serious injury than is a sober individual. More than 40% of fatally injured fall victims have been drinking heavily prior to the accident. In addition, alcohol is thought to be a contributing factor for those individuals sustaining more than one fall during a year.

Drownings

After vehicular accidents and falls, drownings are the third leading cause of accidental death in the United States. The study reports 7,000 drownings were reported for 1980 in the US. Of these, only about 10% took place in pools; the remainder occurred in such other locations as lakes, rivers, and oceans. Alcohol is an undisputed factor in many drownings, as cited in several surveys.

Aviation Accidents

Alcohol consumption by commercial airline pilots is subject to federal control; however, pilots of privately owned light aircraft are free to drink before flying.

"It is not surprising that alcohol consumption has contributed to many fatal crashes involving private pilots, explained Dr. Lowenfels. The Federal Aviation Administration reports that significantly elevated blood alcohol levels are present in about 16% of all fatal light aircraft disasters."

Cold-Associated Injury

According to Dr. Lowenfels, intoxication greatly increases the risk of both exposure-related hypothermia and frostbite. A recent study of 63 exposure-related hypothermia deaths in the District of Columbia found measurable levels of alcohol in 69% of victims.

Homicides and Suicides

Alcohol appears to be implicated in approximately 50% of all homicides in the United States and there

appears to be a similarly strong correlation between alcoholism and suicides. The study reports that 20% of 646 successful suicide victims had blood alcohol levels in excess of 0.10% - evidence of heavy drinking. In an 11-year study of 68 middle-aged male alcoholics, 26 (38%) had made a suicide attempt before the study ended.

"Recognition of the association between alcohol and accidents is important not only for proper care and for treatment of underlying alcoholism, but to stimulate enactment of preventive measures aimed at reducing the risk of alcohol associated injuries," explained Dr. Lowenfels. "The experience in several states tends to confirm that raising the legal drinking age is an effective measure in reducing traffic fatalities."

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- * From an Australian Heart Foundation pamphlet.
- ** Information taken from the US Surgeon General's report: Smoking and Health, 1979.
- *** British Medical Journal, 11th August 1979.



PHYSICIAN TELLS STORY OR 'BABY FAE' TO AMERICAN MEDICAL NEWS

"It's an easy diagnosis to make, and she was only hospitalized overnight. Her parents were given a choicethey could let the child die in the hospital or they could take her home to die. A pediatric cardiologist made the diagnosis... The cardiologist was not sure if we were prepared to move yet on our xenografts, but she alerted me that Baby Fae might be a possible candidate... The university's Institutional Review Board had only the week before made the final decision to proceed. We were prepared to move when a desperate situation presented itself. Baby Fae's parents were notified that one final possibility existed for their child. They were told to think it over and to readmit the child if they were interested."

So spoke Leonard L. Bailey, MD, surgeon responsible for an historic first transplant of a baboon heart to human recipient, to *American Medical News* national affairs editor Dennis L. Breo one week after the event. In exclusive interviews, Bailey and immunologist Sandra Nehlsen-Cannarella, PhD, explained why and how the extraordinary operation at California's Loma Linda University Medical Center took place:

"The underdeveloped left-heart syndrome (affecting Baby Fae) kills one of every four children who die within one week of birth," Bailey said. "I wanted to do something about these cases. The bottom line, believe it or not, is that this xenograft may work. I have always believed it would work... My dilema has been educating the university and the medical profession... I think that Baby Fae is proving that we're in for some interesting revelations. I think that we're onto something important."

Nehlsen-Cannarella explained that the transplant was preceded by six days of meticulous testing of the infant's tissue reactivity against that of six baboons and human controls. Sophisticated tissue-typing protocols enabled the team to select the one baboon to whose tissues Baby Fae demonstrated the least reactivity, allowing a xenograft by scientific forethought rather than by random chance. "Her reaction to this baboon's tissue was only slightly stronger than her reaction to her own parents."

"I believe that science must develop hand-in-hand with ethics," Bailey said. "From the start of this formal project 14 months ago, we have clearly insisted upon a therapeutic intent. This is not simply experimentation for experimentation. We believe we are helping the newborn."

A Loma Linda official said the informed consent document signed by the parents was detailed, appropriate and valid. "Many attorneys looked at this form and we feel very comfortable that Baby Fae's parents knew exactly what they were doing," he said.

REPORT FIRST WORK-EXPOSURE DEATHS FROM ETHYLENE DIBROMIDE

The first report of occupational deaths associated with exposure to ethylene dibromide (EDB) appeared in the *Journal of the American Medical Association*.

Gideon A. Letz, MD, of California's Department of Health Services in Berkeley, and colleagues tell of a worker who collapsed within five minutes after entering an industrial tank that was later found to contain residues of EDB. "He died 12 hours later with metabolic acidosis, depression of the central nervous system and laboratory evidence of liver damage," the researchers say.

"A supervisor attempting to rescue the first victim also collapsed inside the tank and died 64 hours later with intractable metabolic acidosis and liver and kidney failure," they add.

EDB has been a popular fumigant for the past 40 years but has recently become a source of public concern, the researchers point out. Residues of EDB are found in water and food, including fruits, grains and their derived market-basket products. "The public health implications are potentially great because EDB is a potent carcinogen and genotoxin in animals," they say. "Calculation of the exact absorbed amount of EDB is not possible in the cases reported herein. The patients could have inhaled or swallowed EDB. It can be assumed, however, that absorption by the dermal route in these cases was extensive. The air levels that were measured in the tank would not produce acute toxic effects in animals."

The deadly pesticide can cause death in experimental animals when inhaled and when absorbed by the skin. Both routes produce depression of the central nervous system as well as lung, liver and kidney damage.

"The concentration of EDB in the tank fluid were high (0.1 percent to 0.3 percent), and both victims had extensive skin contact with this fluid," the researchers say.

Patients lacked signs of pulmonary damage, but distinctive skin lesions did appear in one of them. The researchers conclude, therefore, that a primarily dermal exposure to a 0.1 percent solution of EDB for brief periods (20 to 60 minutes) was fatal for both men.

JAMA, Nov 2, 1984

AUTO RESTRAINT DEVICES SAVE LIVES OF CHILDREN

The use of child restraint devices in automobiles has reduced the number of childhood motor vehicle fatalities in one state by 50 percent, according to a report in the *Journal of the American Medical Association*. The report documents this type of mortality of children since enactment of the Tennessee Child Passenger Protection Act in 1978. Tennessee was the first state to adopt such legislation.

Michael D. Decker, MD, MPH, of the Centers for Disease Control in Atlanta, and colleagues report that during the years 1978 through 1983, Tennessee traffic accidents caused the death of 81 children younger than 4 years; only two were in child restraint devices. "During this period, as child restraint device use rose from 8 percent to more than 30 percent, the number of deaths among children younger than 4 years declined more than 50 percent," the researchers say.

The study showed that children not in child restraint devices were 11 times more likely to die in accidents than those who were in child restraint devices. The researchers also point out that children who were held in the arms of adults were exposed to a risk of injury or death comparable to that of children left entirely unrestrained.

In a related editorial, Robert S. Sanders, MD, of the Rutherford County Health Department in Murfreesboro, Tenn., and Bruce B. Dan, MD, a JAMA senior editor, note that pediatricians and other physicians played a key role in lobbying for the Tennessee Child Passenger Protection Act. In the 48 other states with similar legislation, physicians have also showed strong support.

"Motor vehicle accidents are the leading cause of death and injury for all children beyond infancy," they point out. "An increasing number of physicians have recognized that the current epidemic of highway casualties among our very young is essentially preventable."

Sanders and Dan add that many physicians and safety advocates believe it is time for state legislatures to help protect older children and adults. They note that the US Department of Transportation has required the gradual introduction of air bags or passive restraint devices into new automobiles unless a significant number of states (representing two thirds of the US population) approve mandatory seat belt laws by April 1989.

JAMA Nov. 9, 1984

LOW BIRTH WEIGHT MAY HAVE GENETIC LINK

Birth weight may be influenced by hereditary factors, according to a recent report in the *Journal of the American Medical Association*.

Mark A. Klebanoff, MD, MPH, and colleagues at the National Institutes of Health, Bethesda, Md., studied a cohort of 1,348 pregnant women and recorded each mother's birth weight before her infant was born. The results showed a strong link between low maternal birth weight and low infant birth weight. Compared with infants of mothers weighing 8 pounds or more at birth, infants of mothers weighing 6 to 7.9 pounds, 4 to 5.9 pounds, and less than 4 pounds were 0.2 pounds, 0.5 pounds, and 0.4 pounds lighter, respectively, the researchers found.

The mean birth weight of infants whose mothers weighed the least (less than four pounds) was 7.1 pounds; the mean for infants whose mothers weighed 4 to 5.9 pounds was 6.8 pounds; and those whose mothers weighed 6 to 7.9 pounds weighed a mean of 7.2 pounds. Mothers who weighed 8 pounds or more at birth had infants with a mean weight of 7.5 pounds, the researchers report. They add that the mothers who weighed less than four pounds at birth were almost certainly preterm, which may explain the apparent discrepancy.

"The data lead us to speculate that factors influencing a mother's own birth weight exert more influence on the rate of intrauterine growth of her offspring than on the duration of gestation," the researchers say. They add that further studies of women of known birth weight and gestational age are needed to determine the role of duration of gestation in the prediction of birth weight.

Besides low birth weight of the mothers, the researchers found several factors related to low birth weight among the infants in the study. These included advanced maternal age, lower prepregnancy weight, smaller pregnancy weight gain, fewer years of schooling, maternal smoking, and infant female sex. After adjusting for these factors, the study showed that compared with mothers who weighed 8 pounds or more at birth, mothers weighing 4 to 5.9 pounds were at 3.46 times the risk of having an infant of low birth weight, and mothers weighing 6 to 7.9 pounds were at 1.66 times the risk.

The researchers conclude that there is a strong relationship between maternal birth weight, both before and after adjusting for multiple variables.

JAMA Nov. 2, 1984

TREAT SCALP CONDITION WITH REDUCTION PROCEDURE

Two dermatologists report in the November Archives of Dermatology on successful treatment of an unusual scalp condition typified by the formation of ridges and furrows and accompanied by patches of baldness. Jerome M. Garden, MD, and June K. Robinson, MD, of Northwestern University School of Medicine in Chicago, describe treatment of cutis verticis gyrata (CVG) with the scalp reduction procedure, a surgical excision of affected scalp and closing with staples. "Scalp reduction generally has become a important technique for the correction of such disorders as cicatricial and other forms of alopecia," the authors say. "Eighteen months after the scalp reduction procedure, there was no noticeable return of the process," they say of the case described.

DAY-CARE CENTER CHILDREN VULNERABLE TO CONTAGIOUS DISEASE

Infants and young children in day-care centers contract *Hemophilus influenzae* type b disease at almost twice the rate as those at home, according to a study reported in the *Journal of the American Medical Association*.

H. influenzae type b is the most common cause of meningitis and epiglottitis in children. It is also one of the most common causes of infection in infants.

Researchers Stephen R. Redmond, MD, of the Monroe County (NY) Department of Health, and Michael E. Pichichero, MD, of the University of Rochester School of Medicine and Dentistry, studied records of all cases of *H. influenzae* disease reported in Monroe County in 1982 and 1983. While *H. influenza* type b meningitis and other invasive disease caused by the organism occurred at a rate of 64.3 per year per 100,000 population aged 0 to 5 years in the non-day-care children, the rate for the same age group in day-care centers was 109.4. Differences were highest in infants younger than 1 year, in whom the risk was 12.3 times greater for day-care center attendees. In the day-care center infants 1 to 2 years old, the risk was 7.2 times greater, and it was 3.8 times greater for those 2 to 3 years old.

For *H. influenzae* type b meningitis, which has a mortality rate of about 10 percent and which leaves neurological problems in about one-third of victims, differences in the rates per 100,000 annually comparing daycare center infants and general population infants not in day care centers were significant: Day-care infants under 1 year had a rate of 877.2 compared with a rate of 86.2 for non-day-care attendees. For infants 1 to 2 years old, rates were 308.0 for day-care attendees and 52.4 for non-attendees. Infants 2 to 3 years old in day-care centers had a 215.7 per 100,000 rate, and those not in day-care centers had a 24.6 rate.

Regarding all *H. influenzae* illnesses in day-care attendees, the researchers say that age-specific attack rates were more than ten times higher than those of non-day-care groups for infants younger than 1 year, and they remained considerably higher in every age group up through the age o 4 years.

The researchers note that the licensed day-care industry is growing as more women obtain employment outside the home. Further study by health departments and physicians of *H. influenzae* type b disease and possible preventive strategies is necesary, they believe.

JAMA Nov. 9, 1984

BETA BLOCKER DRUG CONTROLS MIGRAINE HEADACHES

Persons who suffer frequent migraine headaches may have fewer episodes by taking daily doses of timolol maleate, a beta blocker. The evidence comes from a study of 94 such patients that is reported in the *Journal of the American Medical Association*.

Stanley Stellar, MD, of St. Barnabus Medical Center, Livingston, N.J., and colleagues conducted a 20-week, double-blind crossover study comparing patient response to timolol maleate, 20 to 30 mg per day or matching placebo. After an initial four weeks when all patients received placebo, 47 patients were given timolol maleate for eight weeks while the other 47 were given placebo. During a second eight-week period, the treatments were switched.

"Timolol was significantly better than placebo in terms of decrease in frequency of headaches from baseline, numbers of patients who had a 50 percent reduction in headache frequency, global response, and patient preference," the researchers say. "The study demonstrates that the beta blocker timolol is a safe and effective treatment in patients with frequent migraine headaches."

From a mean baseline level of 6.8 headaches per month, the mean decrease with timolol was 2.5 headaches and the mean decrease with placebo was 1.8. The researchers say that among those patients who showed definite improvement, 65 percent were receiving timolol; 40 percent were receiving placebo. After crossover, those patients switched from placebo to timolol continued to improve, while those switched from timolol to placebo tended to relapse. They add that the duration and severity of headaches that did occur were unchanged, and that few side effects were reported with either timolol or placebo.

The researchers note that since the response in placebo was quite high, great caution should be used in interpreting the results of noncontrolled studies of patients with migraine headache.

In a related editorial, Donald J. Dalessio, MD, of the Scripps Clinic and Research Foundation, La Jolla, Calif., discusses the use of various beta blockers in the prophylaxis of migraine headaches. He notes that one of these, propranolol hydrochloride (commonly used to treat hypertension and heart arrhythmia), has been known to be effective in preventing migraine since the mid-1960s. Dalessio suggests that propranolol, timolol, and other nonselective beta blockers are more effective in treating migraine than are the more cardiac-selective drugs.

JAMA Nov. 9, 1984

REPORT HEPATITIS A OUTBREAK IN NEONATAL UNIT

Infants receiving blood transfusions may be at risk of acquiring hepatitis A virus. According to a report in the *Journal of the American Medical Association*, infants with the virus may show no symptoms and yet transmit it to nurses and others caring for them.

Robert C. Noble, MD, of the University of Kentucky College of Medicine, and colleagues say that 11 newborns in one neonatal intensive care unit were infected by blood from a single donor. This caused an outbreak of 55 cases of hepatitis A, 35 of which were symptomatic. It was later determined that the person who donated the blood had become ill with flulike symptoms and jaundice one week after the donation.

The researchers note that transmission of hepatitis A by transfusion is rare, but that a nursery or neonatal intensive care unit seems to be an ideal for transmission of the virus to personnel or other infants. Blood from one donor is often used for more than one infant and many nurses have contact with the asymptomatic infants, which compounds the problem. In this case, three infants who had not received the infected blood also acquired

asymptomatic hepatitis A, as did six hospital personnel. Symptomatic hepatitis occurred in one physician, ten nurses, eight other hospital staff, eight immediate family members and eight relatives.

In a related editorial, George F. Grady, MD, of the Massachusetts Department of Health, Boston, says, "The appearance of hepatitis A in this setting is the most recent signal that transfusion practices must be under constant reassessment." He adds that studies suggest that newborns have an immunologic vulnerability to hepatitis A, as they do to cytomegalovirus. Antibody for both infections can be detected through blood tests, Grady notes, but there is no test to confirm the presence of active virus. He advises improving staff hygiene practices, reducing the volume of blood transfused whenever possible, and using blood from only one donor for each infant.

In another article in this issue, Bruce S. Klein, MD, of the Centers for Disease Control, Atlanta, and colleagues, describe an outbreak of hepatitis A in a neonatal intensive care unit in Wisconsin that resulted in secondary cases in two other hospitals and in the community. The source for this outbreak was not determined, but the transmission of virus among infants by nurses was suggested.

JAMA Nov. 16, 1984

NEW TEST INDICATES ALZHEIMER'S DISEASE

Positron emission tomography (PET), when used to observe glucose metabolism in the brain, has accurately differentiated persons with Alzheimer's disease from normal elderly subjects. A report in the *Journal of the American Medical Association* describes the noninvasive procedure that promises early recognition of the often debilitating dementia.

Robert P. Friedland, MD, of the Veterans Administration Medical Center in Martinez, Calif., and colleagues measured the metabolism rate of glucose in the brains of two patients with Alzheimer's disease and compared their rates with those of seven healthy controls. All subjects were in their sixties. The two subjects with Alzheimer's showed reduced metabolism of glucose in the temporal-parietal cortex. In both patients this was more pronounced on the right side and was clearly visible on the PET images of their brains. The researchers found that rate of metabolism in this region in normal patients is substantially higher and equal to the rate of metabolism in the frontal cortex.

"These changes have been found in all of 16 other subjects with Alzheimer's disease studied... in our laboratory and are not found in healthy, aged subjects," the researchers say. "Similar findings have also been reported by others."

In the two patients studied, magnetic resonance (MR) and computed tomographic (CT) images revealed moderate ventricular enlargement in one and ventricular enlargement and cortical atrophy in the other. These imaging techniques are also useful in evaluating mental

function, the researchers point out. "While the MR image may not be diagnostic for Alzheimer's disease, it is superior to CT in detecting the presence of multiple strokes as well as delineating atrophic cortex, because of its intrinsically greater contrast sensitivity."

The researchers note that CT has already been used successfully to rule out other illnesses causing dementia, and they say that photon emission CT may also be useful in diagnosing Alzheimer's disease. Their study concludes, however, that PET is the most promising test so far.

JAMA Nov. 16, 1984

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Medicolegal Decisions



HOSPITAL SUED FOR EXCESSIVE RADIATION GIVEN TO 9-YEAR-OLD

A patient's mother was entitled to recover the reasonable value of extraordinary nursing service she rendered to the patient, an Ohio appellate court ruled.

The 9-year-old patient underwent surgery for a malignant brain tumor. Approximately 80 per cent of the tumor mass was removed, and radiation therapy was prescribed. Due to a miscalculation by the physicist who calibrated the radiation equipment, the radiation delivered was about 16 per cent greater than what was prescribed. In addition, the prescribing physician prescribed radiation for the entire brain, rather than concentrating it at the site of the residual tumor. There was conflicting expert testimony as to whether, at the time in question, whole-brain radiation was appropriate medical therapy.

As a result of the radium overdose as well as whole-brain radiation, the patient lost her hair, sustained stunted growth, impediment of speech, and became a quadriplegic paralytic with loss of intellectual functions. In an action against the hospital and the prescribing physician, a trial court awarded the patient \$250,000 compensatory damages against the hospital only. It found the prescribing physician not negligent.

On appeal, the appellate court said that the trial court properly prohibited the patient from presenting testimony on punitive damages. The hospital's failure to assure proper calibration of its Cobalt 60 unit and its later attempts to conceal the amount of excess radiation the patient received did not justify an award of punitive damages. It was inconsistent for the jury to find substantial compensatory damages for the patient and at the same time to award no medical expenses for the injury. The mother presented substantial evidence of medical expenses. The trial court also erred in excluding evidence on the mother's claim for extraordinary nursing services rendered by her to the patient. The mother should be allowed to recover from the hospital her reasonable value of the care rendered to the patient as a result of the negligent injury. The trial court erred in excluding

testimony by a pathologist on what portion of the patient's medical bills were a direct result of the excess radiation.

Finally, the court said that the hospital's concealment of the amount of excess radiation the patient received due to the negligent calibration of its equipment did not make the negligent act a malicious act that could be the basis for punitive damages, the court concluded.—Rouse v. Riverside Methodist Hospital, 459 N.E2d 593 (Ohio Ct. of App., April 12, 1983)

PATIENT WHO UNDERWENT UNSUCCESSFUL ABORTION SUES

The mother of a child born after an unsuccessful abortion could not recover child rearing expenses from the physician who performed the abortion, a New York appellate court ruled.

Under a theory of wrongful conception, the mother sought to recover for pain and suffering, anxiety and mental anguish, medical expenses and loss of future wages. She also sought to recover expenses involved in caring for and rearing the child. A trial court dismissed the claim for child rearing expenses and part of her other claim, and she appealed.

On appeal, the appellate court said that the mother had no cause of action for the ordinary costs of raising a healthy child. She could recover for medical expenses, pain and suffering, and mental distress, but only to the extent that those injuries resulted from the actual or anticipated physical pain and suffering associated with the pregnancy and delivery, the court said.—*Jean-Charles v. Planned Parenthood Association of Mohawk Valley, Inc.*, 471N.Y.S.2d 622 (N.Y.Sup.Ct., App.Div., Jan. 30, 1984)

PATIENT SUES PHYSICIAN FOR UNSUCCESSFUL ABORTION

A patient could not recover expenses for rearing a normal child after an unsuccessful abortion, a New York appellate court ruled.

The patient had a D&C procedure when she was about eight weeks pregnant in order to abort her pregnancy. The operation was unsuccessful, and she later gave birth to a healthy child. She filed a malpractice and breach of contract action against the operating physician. She sought to recover damages for her medical expenses, loss

of employment, emotional distress, and the costs of rearing her child.

On motions by the physician, the trial court dismissed the patient's request for damages for child-rearing expenses and for her psychological injuries allegedly caused by the obligation of bringing up an illegitimate child and for having to apply for public assistance. The court denied the physician's request to dismiss her breach of contract cause of action.

On appeal, the court agreed that the patient had a cause of action against the physician for performing an unsuccessful abortion. She had no obligation to mitigate her damages by submitting to a second abortion procedure where she faced a greater risk to her health. However, expenses incurred by raising a normal, healthy child were not recoverable. Nor could she recover for her alleged psychological trauma of having to raise the illegitimate child and being forced to apply for public assistance.

The court said the patient had no cause of action for breach of contract arising out of the unsuccessful abortion because the physician had not made any express promise to effect an abortion.—Delaney v. Krafte, 470 N.Y.S2d 936 (N.Y.Sup.Ct., App. Div., Jan. 12, 1984)

PATIENT AND WIFE SUE FOR UNSUCCESSFUL VASECTOMY

The parents of a child born after an unsuccessful vasectomy could not recover child-rearing expenses, a New York appellate court ruled.

A physician performed a vasectomy on the patient in May 1978. A hospital pathologist confirmed the success of the operation. The operating surgeon allegedly did not arrange for a postsurgical sperm count. The patient's wife became pregnant and gave birth to a healthy and normal child. The patient then underwent a second vasectomy. A trial court dismissed a claim for child-rearing costs, but unheld the rest of the cause of action against the physician, pathologist, and hospital.

Affirming the decision, the appellate court said that the patient could recover damages for the expense of the second vasectomy and the pain associated with the first one. The court followed the majority of courts in other states in concluding that ordinary child-rearing expenses should be denied. As a matter of public policy, the court said that birth of an unwanted but healthy and normal child was not an injury to the parents.

The patient's wife could recover for physical pain and suffering, and emotional distress from her unanticipated pregnancy, the court said. The father could recover medical expenses and damages for loss of consortium. The court modified the trial court's order to limit the mother's claim for loss of consortium to that resulting from the second vasectomy only.—Weintraub v. Brown, 470 N.Y.S.2d 634 (N.Y.Sup.Ct., App.Div., Dec 30, 1983)

PATIENT AWARDED DAMAGES AGAINST OPHTHALMOLOGIST

Improper admission of evidence in a patient's malpractice action did not prejudice an ophthalmologist's

an Oregon appellate court ruled in affirming a decision for the patient.

The patient was injured when his shotgun discharged accidentally and birdshot was propelled into his eyes. The ophthalmologist provided emergency and follow-up treatment, which failed to restore his vision.

The patient sued the ophthalmologist for malpractice. At the trial, one medical expert testified that with proper care the patient would have had a 50 per cent chance of retaining functional vision. A second expert testified that he would have had a 75 per cent chance, and a third said that prompt action would have increased his chances of recovery.

A fourth expert stated on direct examination that the patient had a 50 per cent chance of retaining useful vision. On redirect examination, he testified from an article in a medical journal that according to a study, persons with eye injuries similar to that of the patient had a 63 per cent chance of regaining functional vision. The jury found the ophthalmologist negligent and awarded the patient \$450,000 in damages.

On appeal, the ophthalmologist argued that the trial court erred in permitting the fourth expert to testify from the medical journal article. The court said that learned treatises should not be admitted as substantive evidence because they might be misunderstood and misapplied. Therefore, the treatise in the present case was improperly admitted as substantive evidence. However, at the point when the expert testified on the basis of the journal, the jury had heard from several experts that the patient had a good chance of retaining useful vision with proper treatment.

The court found no prejudice in the erroneous admission of the evidence and affirmed the trial court's decision.—*Travis v. Unruh*, 674 P.2d 1192 (Ore.Ct of App., Jan. 18, 1984)

PATIENT WHO HAD CATHETER LEFT IN HEART LOSES SUIT

The doctine of res ipsa loquitur was not applicable in a suit to recover for injuries allegedly caused by a catheter left in a patient's body, an Illinois appellate court ruled.

During prepartions to perform a cardiac catheterization with coronary angiogram, two physicians found a 12-inch, size six French catheter in the patient's body. It extended from the iliac vein into one of the heart chambers. A thoracotomy was performed to remove the catheter.

The patient brought an action to recover damages for personal injuries against the hospitals and physicians who had treated his heart condition. However, they were not all involved concurrently. The patient filed a complaint under the doctrine of res ipsa loquitur. The trial court found that the required element of exclusive control of the catheter had not been established and granted summary judgment for each of the parties being sued.

On appeal, the court said that application of res ipsa loquitur required a showing that the patient's injury

resulted from an occurrence that would not ordinarily occur in the absence of negligence, was caused by an instrumentality or agency under the exclusive control of the party being sued, and occurred under circumstances indicating that it was not due to any voluntary act or negligence on the patient's part. The only element that was not satisfied was that of exclusive control.

The court said that in cases of malpractice against multiple parties the doctrine had in the past been held applicable where the parties were in joint control of the agency causing the injury. The present case involved different treatment by different entities at different times in different locations. It was possible that the catheter was inserted by a party not named in the suit.

All of the parties named established that they had no control of the catheter and no knowledge regarding its placement in the patient's body. The patient failed to present evidence to contradict their assertions. Finding that the situation presented was not suited to the doctrine of res ipsa loquitur, the court affirmed the lower court's judgment.—Loizzo v. St. Francis Hospital, 459 N.E.2d 314 (III.App.Ct., Jan 17, 1984)

PATIENT WHO CONTRACTED STAPH INFECTION SUES

A trial court improperly applied the termination of the physician-patient relationship as the accrual date for a medical malpractice cause of action, the Ohio Supreme Court ruled.

A patient was injured in an automobile accident on about June 25, 1979. He was taken to a hospital emergency room, where he was treated by a physician. Allegedly as a result of negligence, he contracted a staphylococcal infection. The patient also claimed that the physician negligently treated the infection and caused additional injuries and complications including staphylococcal endocarditis. The physician last treated the patient on June 28, 1979.

The patient filed suit against the physician more than a year after the termination of the physician-patient relationship. A trial court granted the physician's motion of summary judgment, and an appellate court affirmed

Reversing the decision, the Supreme Court said that the trial court improperly applied the termination of the physician-patient relationship as the time when the malpractice cause of action accrued. Ohio had recently moved to the discovery standard for medical malpractice claims and that standard should be applied to determine when the patient's cause of action accrued, the court said. The case should be remanded to provide the patient an opportunity to show when he actually discovered or should have discovered that his infection was the result of malpractice.—Clark v. Hawkes Hospital of Mt. Carmel, 459 N.E.2d 559 (Ohio Sup.Ct., Feb. 15, 1984)

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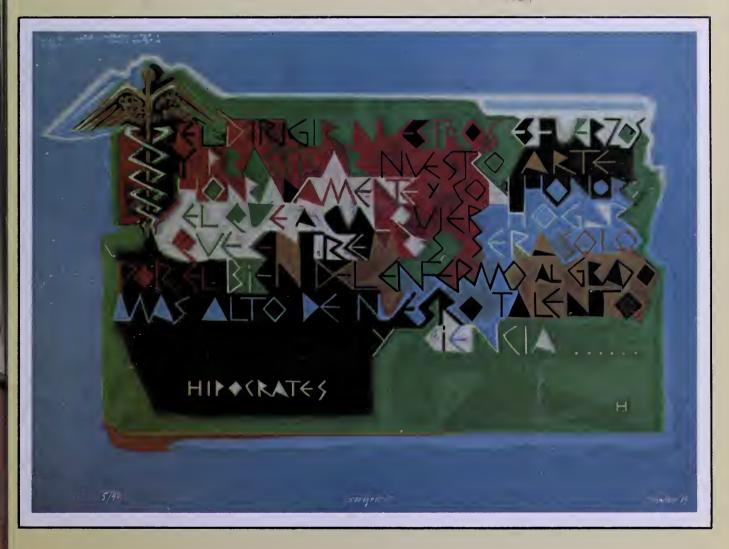
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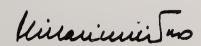
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Columna del Editor



C olamente con leer el contenido de este número Opodemos sentir satisfacción por el trabajo que realiza la Junta Editora en la preparación del Boletín para disfrute y provecho científico de nuestros lectores. Me parece muy dificil que cualquier otra revista médica, con la limitación de recursos que poseemos, logre confeccionar tantos artículos de calidad científica como ésta. Aparecen aquí siete trabajos originales cubriendo seís especialidades médicas. En este caso todos estos trabajos son producto de la experiencia local que junto con la investigación médica nacional cuenta con nuestra revista para su difusión. Nuestra preocupación por la excelencia científica apareada a la calidad gráfica esperamos sirva de estímulo a todos aquellos compañeros que día a día dedican sus mejores esfuerzos al servicio y a la enseñanza. El Editorial no es excepción pues cubre un tema que todos conocemos y nos preocupa, tema que luego de más de veinte años sigue teniendo actualidad y suscitando controversia. Es por eso que invitamos a otras personas a manifestarse sobre ese tema, conocer sus reacciones y las alternativas que puedan aparecer. Quien sabe si la solución al problema planteado en este Editorial proviene de nuestras páginas.



Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico

BOLETIN



VOL 27/NUM 2 FEBRERO 1985

NUESTRA PORTADA

Este mes honra la portada de nuestro Boletín la obra "Homenaje al Médico Puertorriqueño" del insigne maestro don Lorenzo Homar.

La misma fue comisionada por el presidente de la Academia de Médicos de Familia de Puerto Rico, Dr. Richard M. de Andino y obsequiada a la Asociación Médica de Puerto Rico en agradecimiento por la ayuda y cooperación que ha brindado esta organización a la Academia de Médicos de Familia.

La obra capta parte del Juramento de Hipócrates. Sus letras en forma helénica reflejan nuestras raíces griegas. Contrastan los colores azul y verde, los que hacen alusión a los mares Mediterráneo y Caribe, respectivamente.

Agradecemos a don Lorenzo el permitirnos utilizarla en nuestra portada.



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EDITORIAL

Centros Médicos: Servicios y Educación

a finalidad primaria al crear el Centro Médico de Puerto Rico en enero de 1966 fue integrar unos servicios tales como: Salas de Operaciones, Laboratorio, Radiología, Emergencia, Dieta, Vigilancia, Lavandería, Mantenimiento y otros en una misma planta física. Con ello se pretendía lograr abaratar los gastos operacionales. Veinte años más tarde la mayoría de las personas que participan como proveedores o compradores de servicio del Centro Médico de P.R. no están satisfechos con su funcionamiento y eficiencia.

La cantidad y complejidad de emergencias médicas que son atendidas en el Centro Médico de Puerto Rico ha alcanzado un incremento vertiginoso en los últimos años. Los casos de accidentes automovílisticos, agresiones o heridas penetrantes han sido los más frecuentes, de estadías prolongadas muy costosos y la mayoría de las ocasiones asociado con una alta mortalidad. El trauma es la causa principal de muerte desde un año hasta los cuarenta y su asociación al uso del alcohol es generalmente conocida.

Los problemas financieros del Centro Médico se han perpetuado por no habérsele asignado un presupuesto operacional. Los costos para proveer los servicios de excelencia que amerita nuestra población en el Centro Médico han ido en escala ascendente. Las salas de operaciones carecen de personal, de equipo, material y supervisión adecuada. No se ha dado mantenimiento adecuado ni se ha reemplazado el equipo de radiología, de salas de operaciones, unidades de aire acondicionado y otros.

El Hospital Universitario de adultos y el Hospital Pediátrico Universitario son instituciones cautivas del Centro Médico al depender exclusivamente de todos los servicios que éste presta. Estos hospitales son meramente proveedores de camas y servicios de enfermería a los pacientes. Carecen estas dos instituciones de salas de operaciones propias. El número de cancelaciones de intervenciones quirúrgicas en el Centro Médico es exhorbitante con la consiguiente estadía prolongada de los pacientes y la pobre utilización de camas y otros recursos en los hospitales mencionados anteriormente. Debido al volumen, la complejidad y naturaleza de la condición de los pacientes se debe autorizar la construcción de salas de operaciones en ambos hospitales y descentralizar algunos servicios. Estas dos instituciones podrían llevar a cabo

procedimientos de menor envergadura y el Centro Médico se limitaría a casos de mayor complejidad tales como: Cirugía Cardiovascular, Neurocirugía complicada, Ortopedia, Trauma y Quemaduras. La programación electiva en los hospitales de adultos y niños no se vería afectada por las emergencias.

A corto plazo el Gobierno de Puerto Rico debería establecer tres centros de Trauma que sean también centros educativos universitarios asociados a Escuelas de Medicina y localizados en San Juan, Ponce y Mayagüez. A su vez las escuelas de medicina en Ponce y Mayagüez deberían estar afiliadas a universidades privadas o públicas. Se debe adiestrar personal adecuado para evaluar y tratar los pacientes traumatizados. Es también conocido que los residentes en adiestramiento proveen servicio de excelencia y que están capacitados para por lo menos iniciar y muchas veces completar el tratamiento a pacientes traumatizados.

Para el finaciamiento de estos tres centros de servicio y educación y eventualmente investigación la única solución factible sería establecer un arbitrio adicional a los cigarrillos, bebidas alcohólicas y licencias de automóviles. Los fondos recaudados se utilizarían exclusivamente para financiar el funcionamiento de estos tres centros en nuestra Isla. Esta medida no implica un aumento en la burocracia gubernamental, ya que estos fondos recaudados por Hacienda estarían destinados desde su origen al financiamiento de estos tres centros de servicio y educación en Puerto Rico y ésto redundaría en un mejor funcionamiento de los mismos. De no contar con recursos financieros adicionales los tres centros médicos de Puerto Rico y en particular el Centro Médico de San Juan, estarán destinados al fracaso.

Emign Vájny Cuitac 1.).

Enrique Vázquez-Quintana, M.D. Catedrático y Director Departamento de Cirugía Recinto de Ciencias Médicas Universidad de Puerto Rico

FAST AIR... Four different dosage forms and... ☐ Prompt, effective relief of bronchospasm ☐ Excellent bronchoselectivity* ☐ Without the need for blood level testing *Bronchoselectivity means a preference for betay adrenergic receptors, located mainly in the bronchial tissue. This preference is not absolute.

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15 ml, 15 mg/ml (approximately 0.65 mg delivered with each metered dose) Self-help for acute attacks...relief within 1 minute1, lasts up to 5 hours1

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Alupent (metaproterenol sulfate) Alupent (metaproterenol Tablets Metered Dose Inhaler Syrup Labelett Salution Inhalant Solution

Please see following page for brief summary of the prescribing information, including warnings, precautions, and adverse reactions.

**When administered by IPPB

†In repetitive-dosing studies with Alupent Tablets and Alupent MDI, the duration of their effectiveness tended to diminish with time. Present studies are inadequate to explain the divergence in duration of efficacy between single and repetitive dosing.

References:

- 1. Reilly, EB et al. A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. *Curr Ther Res* 1974; **16** No. 8, 759-764.

 2. Data on file at Boehringer Ingelheim Ltd.

Alupent (metaproterenol sulfate)

Bronchodilator

Tablets Metered Dose Inhaler Syrup Inhalant Solution

Alupent® (metaproterenol sulfate)
Bronchodilator

Tablets Metered Dose Inhaler Syrup Inhalant Solution

Contraindications: Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated

Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol

Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed

Pregnancy Teratogenic Effects Pregnancy Category C Alupent, brand of metaproterenol sulfate, has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose, the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose and 31 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent, brand of metaproterenol sulfate, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste

Overdosage: The symptoms of overdosage are those of excessive beta adrenergic stimulation listed under Adverse Reactions. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration

How Supplied: Round, white, scored tablets of 10 and 20 mg in bottles of 100 Metered Dose Inhaler containing 225 mg of metaproterenol sulfate (300 inhalations), 15 mg per ml (approximately 0 65 mg delivered with each metered dose) Cherry-flavored syrup, 10 mg per teaspoonful (5 ml), in 16 oz bottles Inhalant Solution 5% in bottles of 10 ml with accompanying calibrated dropper.

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For complete details, please see full prescribing information



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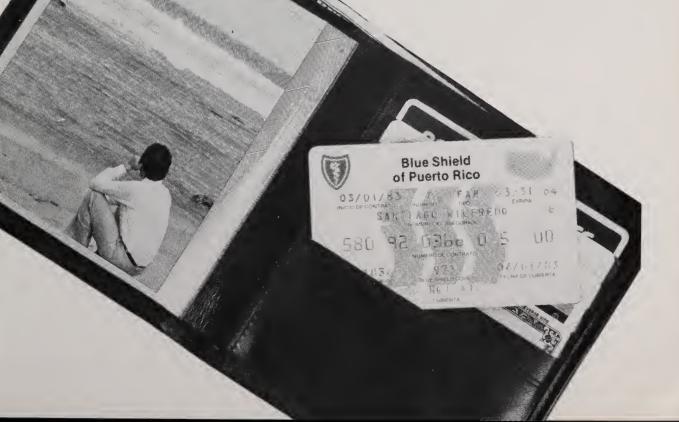
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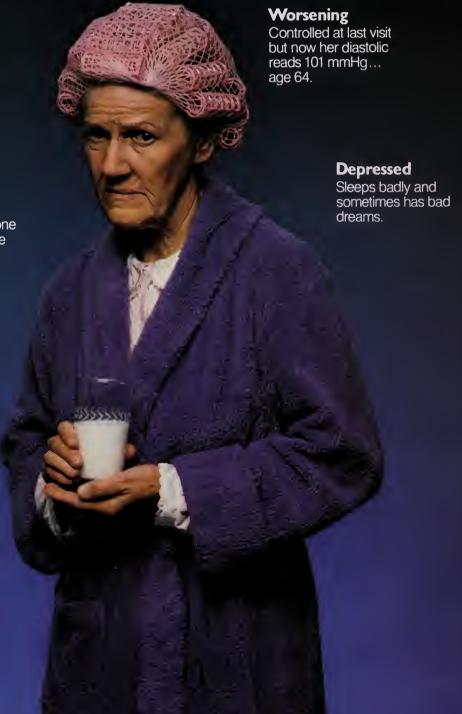
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What can you do for hypertensives like Laura K?



Noncompliant

Frequently misses one or more of her three daily pills.

Lives alone

Doesn't cook much "from scratch." Eats mostly processed foods.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Laura K represents 5,335 women between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.'

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Few CNS effects

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN—making it an excellent choice for patients like Laura K, who may experience CNS effects with other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Laura K...and virtually all your hypertensive patients

TENORMIN® (atendal)





all your hypertensive patients

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) DESCRIPTION: IENDIMIN' (atenciol), a synthetic, beta-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]. Atenciol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37. C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCI (300 mg/ml at 25. C) and less soluble in chloroform (3 mg/ml at 25. C).

INDICATIONS AND USAGE: TENORMIN (atenciol) is indicated in the management of hypertensial that the combined agent agents and the state of the solution o

on. It may be used alone or concomitantly with other antihypertensive agents, particularly with a

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than lirist degree, cardiogenic shock, and overticardiac failure (see WARNINGS). WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered catulously. Both digitalis and atenoid is slow AV conduction. In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and for be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn. It is a patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overl angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physicial activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

drawal symptoms occur
Bronchos postic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta;-stimulating agent (bronchodilator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery in this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and firchloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (e.g. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (e.g. profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients it a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not detay recovery of blood glucose to normal levels. Thyrotoxicosis: Beta-adrenergic blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

monitored closely

Should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with
impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg., reseptine) may have an additive effect
when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine
depletor should therefore be closely observed for evidence of hypotension and/or marked bradyparticularly may report the processors of contracting the processors of the p

cardia which may produce vertigo, syncope, or postural hypotension

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as ingh as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenoloi administration

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-

lation of epithelial cells of Brunner's glands in the duodenum of both male and temale dogs at all tested dose levels of atenoiol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo. letal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since
most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving
atenolol.

atenoiol
Pediatric Use: Safety and effectiveness in children have not been established
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the
patient (U.S. studies) or elicited (eg., by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when
these reactions were volunteered. Where trequency of adverse effects for TENORMIN and placebic
is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency entires the correct progressing that
the stable of the correct progressing the correc

The following adverse-reaction data present frequency estimates in terms of percentages: tirst from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects)

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERYOUS SYSTEM. NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%), PESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)

RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%) TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%) (2%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%) NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tredness (26%-13%), faitique (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%) GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%) RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%) MISCELLANEOUS There have been reported to skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored tollowing cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects or TENORMIN (atenolol)

HENORMINI (atenoiol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by discorientation of time ani place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased pe

formance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis

Other: Reversible alopecia. Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practok reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with over on emergency treatment of overdosage is available. The most common effects expected with over dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotensio bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted. Bradycardia: Alropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker Congestive Heart Failure: Conventional therapy Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or no epinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Aminophylline, isoproterenol, or atropine Hypoglycemia: Intravenous glucose

Hypoglycemia: Intravenous glucose
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a DÖSÄĞE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type duretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significiant accumulation of TENORMIN occurs until creatinne clearance falls below 35 ml. min 1.73 m² (normal range is 100-150 ml/min 1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Atenolol

Elimination Half-lite Creatinine Clearance (ml min 173 m²) Maximum Dosag (hrs) 15-35 <15 16-27 >27 50 mg daily 50 mg every other of

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolot) round, flat, uncoated, white tablets with stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled ro temperature.

References: 1. Data on title, Stuart Pharmaceuticals 2. Herman RL, Lamdin E, Fischetti JL, Ko H Postmarketing evaluation of attenoiol (Tenormin*). A new cardioselective beta-blocker Curr Ther Res 1983; 33(1):165-171 3. Zacharias FJ Comparison of the side effects of different beta block in the treatment of hypertension. Primary Cardiol 1980. 6(suppl 1):86-89



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ESTUDIOS CLINICOS

Acquired Immuno Deficiency Syndrome (AIDS): Experience in the Puerto Rico Medical Center

Consuelo Climent, M.D.* Germán Lasala, M.D.* Román Vélez, M.D.* César Baldizón, M.D.+ María L. Santaella, M.D.§

Abstract: Twenty cases of Acquired Immunodeficiency Syndrome (AIDS) were revised, with clinical immunological and pathological data. Eleven autopsies were performed. The most common diagnoses were *Pneumocystis carinii pneumonia* (15 patients) and Disseminated *Mycobacterium avium intracellulare* (5 patients). Cytomegalovirus was identified in two patients. Kaposi's sarcoma appeared in five patients.

The "Acquired immune deficiency syndrome" (AIDS) is characterized by a severe disturbance of cell-mediated immunity that leads to opportunistic infections or unusual neoplasms, such as Kaposi's sarcoma, in previously healthy individuals. 1-10, 39-44 The disorder has been identified mostly in male homosexuals, but also affects some intravenous drug users, hemophiliacs and sexual partners of patients with AIDS.

In this report we review 20 cases of AIDS and describe the clinical, immunological and pathological findings. Fourteen of those cases died and six were alive at the time of this report. Eleven autopsies were performed.

Materials & Methods

We reviewed the medical records and autopsy protocols of 20 patients with AIDS seen at the University District Hospital, San Juan City Hospital, Oncologic Hospital and Veterans Administration Hospital of Puerto Rico, from April 1982 to December 1983.

Cytological material and histological sections were reviewed from autopsies and slides from previous biopsies and bronchial washings of the 20 patients; 18 had clinical diagnoses of AIDS. The number of hematoxylin and eosin stained slides available for study varied from 2 to 32 per case. In addition, at least one section stained for acid-fast bacilli and a methenamine-silver stain were available in 18 cases. Clinical and morphological data were obtained from the autopsy protocols (in those cases where autopsies were performed) and from the medical records in the remaining cases.

Routine laboratory tests were performed at he University District Hospital and VA Hospital. Immunologic and virology studies were performed at the Immunology section of the Medical Sciences Campus, Department of Pathology, the Laboratory of Clinical Virology, UPR School of Medicine, the Department of Microbiology and the Centers for Disease Control (CDC) in Atlanta, Georgia.

Findings

Patient population

The patients ranged in age form 27 to 54 years (mean 33 years); 18 patients were male and two female (Table I). 13 patients were known homosexuals, 9 were drug addicts and one was both homosexual and a drug addict. One patient had a previous history of a blood transfusion for elective surgery. Abused substances at the time of illness included heroin, cocaine, alcohol and marihuana. All patients were residents of Puerto Rico, although six had traveled to New-York, two to California and one to

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TABLE I

Clinica	al Pro	files of	Pati	ents
Known	Risk	Factors	for	Aids

Patients	Sex	Age	Homosexuality	IV Drug Use	Haltian Origin	Hemophiliac or Blood Transfusion	Occupation	First Dx.	Past Infection
1	М	42		х			Unemployed	New York	Gonorrhea Hepatitis
2	F	33	x	x			Unemployed	New York	
3	М	36	x				Architect	New York	
4	М	27	x				Unemployed	Puerto Rico	Gonorrhea
5	М	40	x				Unemployed	Puerto Rico	
6	М	34	х				Tomato Collector	New York Traveler	Syphilis Gonorrhea
7	М	28	x				Unemployed	Puerto Rico	
8	F	24	x				Unemployed	Puerto Rico	Hepatitis
9	М	28	x				Barman	Puerto Rico	Gonorrhea
10	М	32	x	х			Teacher	Puerto Rico New York Miami	
11	М	38		x		x	Unemployed	New York	
12	М	37		x			Unemployed	Puerto Rico	
13	М	54	x				M.D.	Puerto Rico	Syphilis
14	М	30		x			Unemployed	Puerto Rico	
15	М	34		x			Unemployed	Puerto Rico	Hepatitis
16	М	36	X				Unemployed	U.S.A.	Hepatitis Syphilis Gonorrhea
17	М	41	x				Teacher		
18	М	32	x				Salesman	Puerto Rico California Traveler	Gonorrhea
19	М	34		x			Unemployed	Puerto Rico Post Mortem	
20	М	37		х				Puerto Rico Traveler New York	Syphilis

Florida. Six patients had a previous history of Gonorrhea, four of syphilis and four of viral hepatitis.

Clinical illness

The average duration of illness for the group was 4 months, ranging from two weeks to ten months. (Table II). Fever and weight loss were the more common clinical findings; prominent pulmonary symptoms were a common finding (Table III). Pneumocystis carinii pneumonia (Table III) was the most commonly diagnosed opportunistic pulmonary infection, with morphological identification of this agent in 15 patients (75%). The diagnosis was male from bronchial washings, transbronchial biopsies and postmortem examination. Four patients showed the presence of systemic cytomegalovirus and five disseminated atypical mycobacteria. Kaposi's sarcoma appeared in five of our patients (25%).

Immunologic studies

Table IV summarizes the findings of the lymphocyte subset analysis, proliferative studies and immunoglobulin determinations.

Immunoglobulins - Levels of immunoglobulins were determined in 4 of the 20 patients; the four patients had elevation of at least one immunoglobulin. IgA was the most commonly elevated immunoglobulin in our cases.

Quantitation and immunologic analysis of circulation lymphocytes - Complete blood counts and differentials on the blood of our patients revealed that leukopenia was present in 9 patients. The rest of the patients showed values within normal limits. Peripheral T-lymphocytes were decreased in 8 out of 9 patients. Subtyping of T-cells revealed a decreased Helper-suppressor ratio in 9 patients. One patient had low-normal values, with

20 Fever, Cough,

Expectoration

Weight loss

TABLE II

-		TABLE I	1	
	Clir	nical Profile of	Patients	
Pat	tient Signs and Symptoms	Onset of Itlness (Months)	Infectious Agents	Kaposi's Sarcoma
1	Cough, Respiratory distress, Diarrhea	1	P. Cannii pneumonia	
2	Cough, Fever Anorexia, Weight Loss	10	P.Carinii pneum. Disseminated Mycobacteria avium intracellulare	
3	Anorexia Weight Loss Diarrhea	8	Disseminated Myco- bacteria avium intracellulare. P. Cannii pneum.	
4	Anorexia, Diarrhea, Cutaneous lesions	4	Disseminated Atypical mycobacteria P. Cannii pneumonia	Yes skin Spleen Lymph-Nodes
5	Fever Diarrhea Dysarthria	1	Systemic Cytome- galovirus P. carinu pneum. Esophageal candidiasis	
6	Fever, Weight loss, Diarrhea Lymphadenopathy	8	P. Cannii pneumonia	
7	Diarrhea, Anorexia, Fever, Weight loss Weakness of left leg	6	Systemic Cytomegalovirus	
8	Weakness, Fever, Weight loss, Non-productive cough	6	Mycobacten um avium-intracellulare Rectal candidiasis	
9	Purplish nodules in the skin (face, chest, back)	4	Giardia lambdia pneumonia	Yes, skin
10	Fever, Weight loss, Lymphadenopathy	3		Yes, skin (abdomen)
11	Cough, Dyspnea Weight loss, Fever	5	P. carinii pneumonia	Yes, Lymph nodes
12	Fever, Weight loss	3	P. carinii pneumonia	
13	Anorexia, Fever Diarrhea, Weight loss	6	Systemic cytome- galovirus P. carinii pneumonia	
14	Fever, Cough Weight loss	3	P. carınii pneumonia	
15	Fever, Dyspnea, Cough, White expectoration Weight loss	2	P. carinü pneumonia	
16	Weakness, Dyspnea Weight loss	1	P. carinii pneum. Disseminated atypical mycobacteria	
17	Fever, Diarrhea, Lymphadenopathy Cutaneous lesions	2 week	Systemic cytomegalovirus Toxoplasmosis	Yes, (skin)
18	Fever, Cough, White expectoration, Anorexia, Diarrhea, Weight loss	1	P. carinu pneumonia	
19	Weight loss Fever, Dyspnea,	3 week	Rectal candidiasis P. carinii	
	Cough, Expectoration, Diarrhea		pneum onia	

P. carınii

one um onia

decreased helper subpopulation and relative increase of suppressor subpopulation (Case 17). Leukocyte function tests were performed in 10 patients and were markedly suppressed in their proliferative response to both pokeweek mitogen and phytohemagglutinin.

TABLE III

Symptoms				
	Number			
Fever	15	75		
Weight loss	14	70		
Cough	9	45		
Diarrhea	9	45		
Anorexia	6	30		
Dyspnea	5	25		
White expectoration	4	20		
Cutaneous lesions (Kaposi's)	4	20		
Lymphadenopathy	3	15		
Weakness	3	15		
Disartria	1	5		

Postmortem findings

At postmortem examination of 11 patients, the most common finding (Table V) was *Pneumocystis carinii* pneumonia in 9 patients, followed by disseminated atypical mycobacterial (4 patients) and cytomegalovirus infection (2 patients).

Pneumocystis carinii pneumonia was diagnosed during the course of their disease in 6 patients by cytologic preparations of bronchial washings. In three patients the diagnosis was made in post mortem examination. Cytomegalovirus (CMV) infection was disseminated in the two patients and always affected two or more organs. In the two patients the diagnosis was made at autopsy. The intracytoplasmic inclusions of CMV were seen in the two cases in meninges, and cerebrum. In one case they were also seen in the gastrointestinal tract and the second case showed CMV also in lung, peripheral nervous system, myocardium and adrenals.

Disseminated atypical mycobacteria were identified in 4 patients (all of them) post mortem. The infection involved the lungs, liver, spleen, pancreas, and adrenals in two patients. In the other patients the brain, skin, mediastinal lymph nodes and kidney were involved.

Only one patient in which a post mortem examination was performed had Kaposi's sarcoma. The diagnosis had been made clinically before death by skin biopsy, and after autopsy involvement of lymph nodes and spleen was also demonstrated. These lesions at autopsy did not appear to contribute significantly the demise of the patient.

Other important diagnoses were oral and esophageal candidiasis in two cases, and sepsys due to Salmonella group B organisms in one patient.

TABLE IV

				Laborat	ory Findings					
Case No.	Total WBC/mm³	Total T cells %	Total B cells %	Stimu- lation index %	Helper Sub-Popu- lation	Supressor Sub-Popu- lation	H/S ratio	mg/dl IgG	IgA	IgM
1	3.300									
2	2.400	30	9		4	10	0.25	900	540	175
3	4.600									
4	6.700									
5		36	13	6.32	16	21	0.76			
6	6.000									
7	3.550	35	11	6.13	6	34	0.18			
8 9	1.500	-	-	40.5	6	27	0.22			
	4.130	40	2	8.7	9	40	0.23			
10	2.500			5.38	4	59	0.07			
11	2.400	392	49							
12	1.400	29	17	0.63	13	21	0.62	2.030	120	486
13	3.800	68	23					895	513	85.4
14	2.200	8	1	4.17	1	3	0.33			
15	6.500	17	0	5.54	5	21	0.24			
16	7.800			22.9						
17	7.800	26	17	22.9	24	20	1.2			
18	7.200							1.360	614	118
19	6.300									
20	3.200									

The lymph nodes in all patients displayed a pattern of depletion with atrophic follicles. This picture was not observed when the lymph nodes exhibited involvement by neoplasm or an infectious process. The thymus was not identified in any patient.

TABLE V

Post Mortem Findings				
Patient	P carinii	Atypic al mi coba cteria	CMV	Others
1	+			Salmonella Group B (Blood)
2	+	+		Oral candidiasis
3	+	+		
4	+	+		Kaposi's sarcoma
5	+		+	Esophogeal candidiasis
6	+			
7			+	
8		+		Oral candidiasis
18	+			
19	+			
20	+			

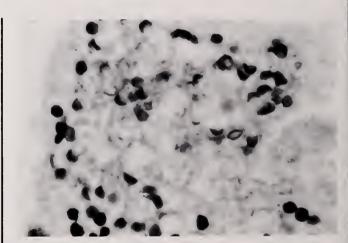


Figure 1. Pneumocystis carinii in alveolar exudate. Grocott's stain.

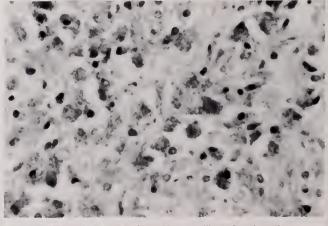


Figure 2. Kaposi's sarcoma. Skin. Hematoxiiin and eosin stain.

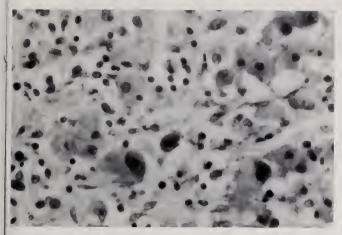


Figure 3. Intranuclear inclusions of CMV. Hematoxilin - eosin stain.

Discussion

In our series of 20 Puerto Rican patients, eleven of which were autopsied, the risk factors previously iden tified in other series were corroborated, i.e., a history of homosexuality, drug addition and blood transusion. The majority of our cases had residence in the USA (New York, California, Florida) at some time before or during the onset of their illness.

The infectious agent most commonly identified was *Pneumocystis carinii*; other infections in order of frequency were disseminated cytomegalovirus and atypical mycobacterial infections.

The average duration of illness in our series was 4 months. The clinical manifestations paralleled those described in the literature, with opportunitistic infections being the most frequent one.

The immunological profile of our cases is consistent with the data obtained in other series in term of the following parameters; decreased or absent delayed hypersensitivity, diminished T lymphocyte responsiveness to mitogens in vitro and decreased Th/Ts ratio.

Pneumocystis carinii pneumonia was the most common diagnosis in our series (15 cases). In 12 patients the diagnosis had been established before death either by biopsy or cytology; in three cases the diagnosis was made at the time of autopsy. The high incidence of Pneumocystis carinii pneumonia has been well documented in the literature and is one of the major diagnostic criteria for this syndrome.

Five of our patients had disseminated Mycobacterium avium intracellulare (MAC) infection. In our series the combination of Pneumocystis carinii pneumonia and MAC was quite frequent. The particular susceptibility of AIDS patients to this organism has been recently documented in the literature.¹¹⁻¹⁶

The patients characteristically have had disseminated disease involving most frequently the lungs, spleen, and lymph nodes, but the bone marrow, the brain, adrenal glands, liver and gastrointestinal tract are also frequently involved. The diagnosis was in most cases made at post mortem examination (4 patients in our series). The pathology of MAC infection often is characterized by

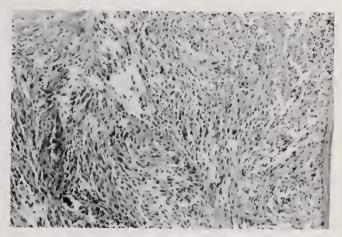


Figure 4. Macrophages in lymph node packed with Mycobacterium avium intracellulare. Acid - fast stain.

poor tissue response with an infiltrate of foamy macrophages packed with acid-fast bacilli. This is of practical importance because tissues that are only slightly abnormal can be packed with infections organisms. Therefore, the pathologist is obliged to perform special staining procedures to uncover the organisms, even in the abscence of the characteristic tissue abonormalities produced by mycobacteria.¹⁷

Surprisingly, in this series the cytomegalovirus was not as frequent as in other series.^{17, 18, 19, 45} Cytomegalovirus was present in only two cases at autopsy and in two patients who died but in whom autopsies were not performed. The organ most commonly involved was the brain and meninges followed by lungs, gastrointestinal tract, peripheral nervous system, myocardium and adrenals.

Kaposi's sarcoma is the neoplasm that most commonly affects patients with AIDS.²⁰⁻³³ In our series, five patients had Kaposi's sarcoma, and only one of these cases had a post mortem examination. In the others the diagnosis was made by lymph node biopsy. One patient had nodal Kaposi's sarcoma with no skin involvement. One patient in our series was diagnosed as Toxoplasmosis by serology, but a post mortem examination was not carried out.

The histopathologic features of lymph nodes in AIDS are presented in several recent publications.³⁴⁻³⁹ The lymph nodes identified in our cases showed lymphoid depletion with absent or very inconspicuous follicles and replacement by a population of small lymphocytes. This lymph node architecture may represent immunologic extenuation due to repeated systemic infectious and neoplasms and may imply a grave prognosis.

In summary, in this study 20 AIDS patients, residents of Puerto Rico, are presented. The risk factors, immunologic deficiency and pathological findings identified in other series were corroborated. These findings underscore the complicated nature of the disease and the need to be wary of multiple opportunistic agents when evaluating pathological specimens from such patients.

Acknowledgment

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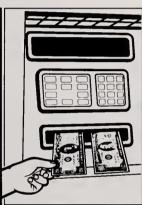
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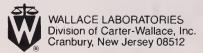
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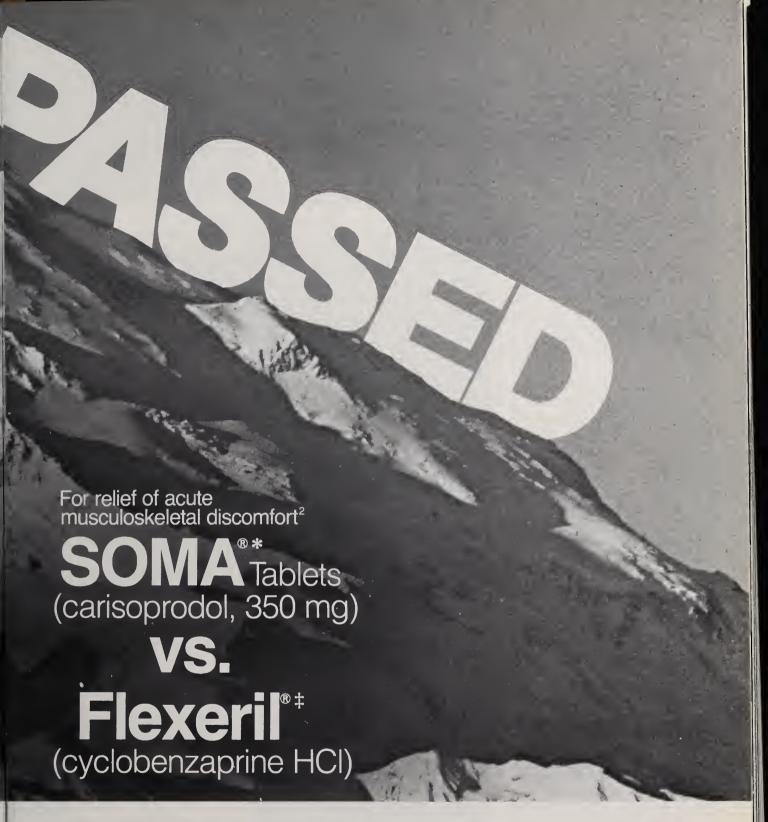
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References: 1. Boyles WF, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions: thoracolumbar strain or sprain. *Today's Therapeutic Trends*, vol. 1(1), 1983. A controlled double-blind study of 71 patients. 2. Rollings HE, Glassman JM, Soyka JP: Management of acute musculoskeletal conditions. conditions-thoracolumbar strain or sprain: A doubleblind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. *Curr Ther Res*, vol. 34, Dec. 1983. A controlled doubleblind study of 58 patients.

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Before prescribing 'Soma', consult package circular or latest PDR information, a brief

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INDICATIONS: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

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hospitalization, may be necessary.

Pregnancy and Lactation: Safe use has not been established; weigh potential benefits against potential hazards during pregnancy and lactation or in women of childbearing potential. Usage in Children: 'Soma' - Not recommended under age 12.

Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g.,

driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive. Drug Dependence: Use caution in addictionprone patients

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of cariso-

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances. Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock.

DOSAGE AND ADMINISTRATION: Adults One 350 mg tablet 3 times daily and at bedtime. OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used successfully with related drug, meprobamate. **HOW SUPPLIED:** White, 350 mg tablets in bottles of 100 (NDC 0037-2001-01) and 500

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Cryptococcai Meningitis

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Abstract: Cryptococcosis is a mycotic disease of man and animals, usually caused by Cryptococcus neoformans. The most serious cryptococcal infections occur in individuals with defective cell-mediated immunity; but, approximately 50% of the patients with cryptococcus central nervous system infection has no known form of immune deficiency. Many patients have a history of antecedent pulmonary infection which rapidly resolved with minimal symptoms. The disease may spread by hematogenous dissemination to almost all organs, particularly the central nervous system. The evolution of meningitis is subacute or chronic where clinical manifestations become apparent over several weeks.

The diagnosis of central nervous system cryptoccocosis in many cases needs to be made on the basis of CSF cultures and/or immunological detection. The testing for cryptococcal polysaccharide capsular antigen is the most important serological aid in the diagnosis of cryptococcal meningitis. Anticryptococcal capsular antibodies are less specific. Several antimycotic therapies have been tried, but the combination of amphotericin B with flucytosine appears to be superior than amphotericin B as a single agent. The combination therapy produces fewer side effects, failures to therapy or relapses, though the mortality rate is not significantly different.

ryptococcal meningitis is a chronic, subacute or rarely acute disease caused by the yeast Cryptococcus neoformans. Known in Europe as the signal disease (malade signal) as it signals an underlying debilitating disease. As the population of individuals with "natural" and iatrogenic alterations in host defenses has increased, the frequency of cryptococcal infections has also increased.

The intention of this article is to review current concepts in epidemiology, host-parasite relationship, clinical manifestations and diagnostic principles. Finally, some prognostic factors and therapeutic management in cryptococcal meningitis will be presented.

Epidemiology

Cryptococcus neoformans is widely distributed in nature^{1, 2} but it is most commonly found in the pigeon excreta.3-5 The pigeon as a symbol of urban decay appears to be the most important vector for the distribution and maintenance of this organism. Areas of accumulated filth and debris of pigeon roosts such as cornices, cupolas and attics of old buildings have been sites of frequent recovery of cryptococcus. This area provides a desiccated environment with alkaline medium, high-nitrogen and high salt substrate.⁶ This particular ecologic niche maintains a restricted environmental habitat to avoid competition with other organisms. If this infected debris is mixed with soil, this organism will be unable to survive. 6 Cryptococcus has been found in areas inhabited by pigeons as rural barn lofts and haymows. The dust in these areas contains viable virulent organisms.7

The average body temperature of the pigeon is 42°C; this makes the pigeon resistant to infection by cryptococcus, but it survives passage through the gut. *Cryptococcus neoformans* can remain viable for two or more years in moist or desiccated pigeon excreta. 6

Although cryptococcosis has been reported in many species of animals, there is no evidence to suggest direct transmission from animal to animal or animal to man. Cryptococcus neoformans in saprophytis environments is basically nonencapsulated, but following acquisition of the polysaccharide capsule such strains and uncapsulated mutants do become virulent. It appears that the potential for developing capsules is a significant virulence factor.

The most common etiological agent described producing cryptococcal meningitis or other form of cryptococcosis is *Cryptococcus neoformans*; however, some other

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species of the genus cryptococcus such as *Cryptococcus albidus*, ¹⁴ have been implicated in human disease from time to time.

There has not been any significant difference in cryptococcal meningitis that can be related to age, race, or occupation. However, pigeon fanciers have a higher than normal occurrence of antibody against cryptococcus, but not a higher incidence of disease. ¹², ¹⁵ It has been more often reported in males than in females. Some authors have suggested for this difference, exposure or hormonal differences as has been suggested for other mycoses. ¹⁵ Recent studies does not show this male predominance.

Host Defense vs. Parasite Virulence

The host responses to cryptococcal infection can be considered as a spectrum. This can range from colonization of the airways¹³ or a symptomatic infections in laboratory workers¹⁷ to fatal cases of disseminated cryptococcosis or meningitis.¹⁸, ¹⁹ Some differences in virulence from various strains for animals²⁰ and possibly for man²¹ have been described, the crucial factor in the outcome of the infection is the immune status of the host. The most serious cryptococcal infections occur in individuals with defective cell-mediated immunity. Impairment of cell-mediated immunity (CMI) in which *C. neoformans* has been frequently described included corticosteroid treatment (i.e. prednisone),²⁵⁻²⁷ organ transplantation (i.e. renal transplant),²⁸⁻³⁰ sarcoidosis,¹⁹ reticuloendothelial malignancy (i.e. Hodgkin's disease),³¹⁻³³ and acquired-immune deficiency.³⁴

Specific abnormalities in CMI in patients with cryptococcus infection included inappropriately depressed skin test response to cryptococcin and mumps; in the leukocyte migration inhibition assay there were depressed group migration inhibition to whole killed *C. neoformans* and soluble cryptococcin³⁵ and decreased lymphocyte transformation upon exposure to whole killed cryptococcus as antigen.¹⁸

In some reports,^{19, 22} approximately 50% of the patients had no known form of immune deficiency, but in most studies a selective impairment of lymphocyte responses to cryptococci has been found.^{18, 23, 24}

After this gross view of epidemiological factors governing *C. neoformans* distribution and after establishing the "type" of patients in which most probably cryptococcal meningitis will be encounter (i.e. impaired immune status), the clinical aspects of the disease will be reviewed.

The Clinical Disease

With rare exceptions the portal of entry of *C. neoformans* is via the lungs following airborne exposure and inhalation of the yeast.⁷ The primary pulmonary infection in a "normal" host is rapidly resolved with minimal symptoms and the disease, if any, is subclinical. In the cases where the host defenses are minimal or inadequate, the disease readily spreads by hematogenous dissemination³⁶ to almost all organs, particularly the central nervous system (mainly the meninges); this can occur in spite of resolution of the lung lesion. For this

reason, it is often difficult to assess the site of the initial infection. Up to day the specific reasons for the predilection for the CNS has not been completely established.⁷

Following meningeal involvement, the evolution of meningitis is subacute or chronic where the clinical manifestations are insidious in onset becoming apparent over several weeks rather than a few hours or days.

The commonest presenting symptom of cryptococcal meningitis is headache mainly localized at the frontal area; occasionally it is temporal and less common occipital or generalized. It may be mild to severe, dull to sharp and gradual to sudden. The next most common symptom is change in mental status; in order of frequency this change includes confusion, personality changes, memory impairment, agitation and less common, psychosis. Eye symptoms may be present including blurred vision, retrobulbar pain, diplopia, and photophobia. 37-38

It should be kept in mind that CNS symptoms may not be present and, if present, they may be so subtle that will not direct or attention to meningitis.

Signs of cryptococcal meningitis do not differ with meningitis of other etiology. Classical signs of meningeal irritation may be present, nuchal rigidity, tenderness of neck, positive Kerning and Brudzinski signs. Fever can be or not present, frequently it is low grade.⁷, ³⁶, ³⁷

The possible exception with cryptococcal meningitis to other etiologies is the presence of increased intracranial pressure by the presence of a single expanding intracranial mass (single cryptococcal granuloma in the brain present with the meningitis), producing nausea, vomiting, papilledema, hemiparesis, paralysis or even coma.³⁷⁻³⁸

Other manifestations that have been described include ataxia, aphasia, slurred speech, paresthesias, seizures, weight loss, incontinence or retention of urine or stools, dizziness and abdominal pain. Involvement of cranial nerves specially III, VI, VII has also been described.³⁸

Diagnosis

The most important method of diagnosis of cryptococcal meningitis is the careful analysis of the cerebrospinal fluid (CSF). The most common patterns of opening pressure, cell counts and cell type, protein, and glucose levels, as found by various authors, is summarized in Table I.

The variations in CSF findings as described are largely a function of time the disease has been present but, in general, the majority of the patients manifest during the course of the disease elevated CSF pressure, moderated leukocytosis with lymphocytic predominance, low glucose and high protein levels.

Cryptococcus neoformans may be scarce or numerous in the CSF, and a India ink examination usually confirms the clinical diagnosis. Results from Butler et al, reveal that only 57% of proven by culture cryptococcal meningitis were positive for India ink preparation. Approximately the same percent (56%) of India ink preparation was positive in culture for cryptococcal meningitis in other studies.³⁷

The lack of specific patterns on clinical grounds and CSF findings in many cases requires that the final

TABLE I

Author (s)	Opening Pressure	White Blood Count	Type of Cell	Protein Levels (mg%)	Glucose Levels (mg%
Butler et al (37)	64% of patients with increased (over normal) pressure Range: 200-400	Range: 0-800 cells/mm³ (97% of patients had values greater than normal)	Range: 8-100% lymphocytes 40% patients had 95 of lymphocytes 60% of patients had 59% or more of lymphocytic predominance	Range 50-300 90% of patients had increased values.	Median: 33 55% of patients with 40 or less 13% of patients with 10 or less
M.T. Stocktill, C.A. Kaufman (38)	Average: 255 Range: 22-500	Range from 2-1,070 cells/mm	Mainly lymphocytic predominance	Average 21 Range: 30-	Express as glucose of CSF/Serum ratio .3 average, range 17
H. Thadepalli (39)	Not available or described	Range from 25-500 cells/mm	More than 80% are are lymphocytes Early in the course of the disease PMN may predominate	85% increased levels	50% of patients with levels of 40 or greater
J.W. Rippon (6)	Not described	Increased, not over 800 cells/mm	Lymphocytic predominance	Range from 40-600	From normal to to 10 or less

diagnosis of cryptococcal meningitis needs to be made on the basis of CSF cultures and/or immunological detection.

Cultures of CSF for Crypotococcus neoformans has a mean delay until growth of three to four days and although this can delay specific therapeutic intervention, today is one of the most reliable final diagnostic tools available. To speed up final diagnosis and to determinate prognostic factors, there are specific immunological tests available.

Immunological Diagnosis of Cryptococcal meningitis

The chemical structure and antigenic nature of *C. neoformans*, particularly the capsule, have been subject of much investigation. In 1949, Evans divided the pathogenic strains of *C. neoformans* into three serologic types: A, B, and C based on capsular material. The capsular material is composed of a polysaccharide of mannose, xylose, and a uroconic acid (probably of glucoronic acid). Several studies of serologic group distribution indicate that essentially all organisms from avian habitat and human infections are type A.⁴⁴⁻⁴⁶

The testing for cryptococcal polysaccharide capsular antigen is the most important serological aid in the diagnosis of cryptococcal meningitis. The antigen is most often sought in the CSF; however, any body fluid may be assayed for its presence. Many methods successfully detect cryptococcal antigen including latex agglutination inhibition card test (Latex), complement fixation (CF), counter immunoelectrophoresis, and enzyme linked immunosorbent assay (ELISA). Due to highly sensitivity and rapidity the Latex test is recommended actually for widespread laboratory use.⁴⁷⁻⁵⁰ Actually reliable commercial Latex test kits are available.⁴⁷ Nonspecific

agglutination reactions caused by the presence of rheumatoid factor require that the Latex test includes a control for its detection. The Latex method has detected cryptococcal antigen in 94% of CSF and 70% of serum samples in cases of proved cryptococcal meningitis, and positive serum samples occuring in almost all the patients with positive CSF samples. One important feature of the Latex test is that the diagnosis of cryptococcal meningitis can be made in smear and culture negative cases.

Some important points to remember in the interpretation of the Latex test for capsular antigen in the CSF are:

- Latex titers of 1:8 or more in the proper clinical setting are diagnostic.⁴⁷
- Latex titers of less than 1:8 are considered highly suggestive of cryptococcal meningitis. 48
- False-positive reactions are not common, the titers are less than 1:8 and they have been described in cases of CNS malignant neoplasm, bacterial meningitis, and a single case of osteomyelitis with paravertebral abscess by Klebsiella. 48, 49, 57, 58
- False-negative reactions can occur in patients with prolonged illness or in patients with very early infections with positive cultures and no other abnormalities detectable.⁵¹
- If a patient is highly suspected to have cryptococcal meningitis, do not rule out this possibility with a single negative test; repeated testing is strongly advised. ⁵¹ A negative reaction at low dilutions with a specimen of high antigen titers may occur (the prozone phenomenon).

Anticryptococcal capsular antibodies actually are not recommended because of frequent false-negative and false-positive reactions. 59-62 One example of these find-

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ings are the studies of Henderson, Bennet and Haber, by which they found that using a sensitive RIA, anticryptococcal antibodies were detectable in 89% of 185 normal volunteers and only 41% of 51 patients cured of cryptococcal meningitis.⁵⁹ In the same studies, 8 cured patients vaccinated with purified cryptococcal capsular antigen manifested a significantly blunted response when compared with vaccinated normal volunteers. These studies suggest that actual detection of cryptococcal antibodies has limited usefulness in the diagnosis of cryptococcal infections.

Prognostic Factors in Cryptococcal Meningitis

The studies of Diamond and Bennett⁵⁹ correlating clinical and laboratory findings in 3 cases of cryptococcal meningitis before and after treatment with amphotericin B, determinated some important prognostic factors that will be presented next.

Patients who died of active disease during treatment considered at significant risk or with poor prognosis had: positive initial CSF India ink for C. neoformans, high initial CSF opening pressure, low initial CSF glucose levels, initial CSF leukocytes less than 20/cc, cryptococci cultured from blood, sputum, stool, urine or other extraneural site (especially more than one of these), absent anticryptococcal antibody, initial CSF or serum cryptococcal antigen titer 1:32 or higher and corticosteroid therapy or lymphoreticular malignancy. Those who failed after treatment had: CSF glucose levels abnormal during 4 weeks or more after starting therapy, initial CSF leukocytes less than 20/cc, cryptococci cultured from blood, sputum, or stools or specially from more than one extraneural site, absent anticryptococcal antibody postreatment CSF or serum cryptococcal antigen titers 1:8 or more, no significant decrease in CSF or serum titers during therapy and daily corticosteroid therapy equivalent to 20 mg of prednisone or more after completion of antifungal therapy.

In other series, ³⁶, ³⁷, ⁶³ cryptococcemia was an extremely grave prognostic sign. Also, poor prognosis and increased risk for relapse has been documented when there are very high levels (1:32 or more) of antigen titers in CSF before therapy and persistence of titers greater than 1:8 after therapy in more recent studies by Bennett et al.⁶⁴

Treatment

Before the introduction of amphotericin B the course of untreated cryptococcal meningitis was a uniformly fatal disease (75% of patients die within one year after its onset). Following introduction of amphotericin B only 53% to 60% of survival rates has been achieved usually with repeated therapy, prolonged treatment and substantial toxicity, 59, 65, 67 but the low proportion of cures and secondary drug resistance make this drug non-desirable as a single agent. 68

The combined therapy of amphotericin B and flucytosine has been found to be a superior treatment. This treatment allowed the use of a lower and less toxic dose of amphotericin B with more rapid sterilization of the CSF and the reduced duration of treatment.⁶⁴

Alternative anticryptococcal drugs that presently are being evaluated in humans include the imidazole derivatives. One of these derivatives included miconazole with an actual experience in the treatment of cryptococcal meningitis of both successes⁶⁸, ⁶⁹ and failures.⁷¹

The drug regimens to be described are based on the protocol regimens used by Bennett et al⁶⁴ in comparison studies of amphotericin B as a single agent vs. combination with flucytosine in the treatment of cryptococcal meningitis.

The treatment using amphotericin B as a single agent consist of a 10-week regimen of 0.4 mg/kg of body weight per day. The combined treatment consists of a 6-week regimen of amphotericin B, dose 0.3 mg/kg per day and flucytosine, dose 150 mg/kg per day divided in six hourly doses. The dosage scheduled for flucytosine (5-Flurocytosine) are based on proposed guidelines that modify the patients dosage if renal impairment is determinated using creatinine clearance as an indicator⁷³ (See Table II).

There are some adverse reactions in the use of these drugs that should be mentioned. Amphotericin B: following IV administration the patient can experience chills, sweats, fever, myalgia, anorexia, nausea, vomiting and headaches. Anemia often occurs during prolonged therapy (0.5 mg/kg for 4 weeks or more). Evidence of renal damage may be manifested by most of the patients, but permanent damage has been reported

TABLE II

Dosage Schedules for Flucytosine Using Creatinine Clearance As an Indicator of Renal Function			
Creatinine Clearance (ml/min)	Individual Dose (mg/kg)	Dose Intervals (hours)	Daily Dos (mg/kg)
Greater than 40	25-50	6	100-200
40-20	25-50	12	50-100
20-10	25-50	24	25-50
Less than 10	50	More than 24*	

^{*}From Schonebeck J, Polak A, Fernex M, et al (72).

^{**}Intervals based on serum levels of Flucytosine which must be measured regularly.

especially when the total dosages exceeded 3gm. and therapy has been prolonged. Hypokalemia is common and potassium levels should be determinated at least twice weekly.⁶³

One point to remember is that amphotericin B is excreted primarily in the bile and since urinary excretion is of minor importance, renal insufficiency does not appreciably influence serum levels.

Concerning flucytosine, the most common and important adverse reactions are leukopenia, thrombocytopenia and anemia, which are reversible, and diarrhea, usually associated with abdominal cramps, vomiting and the presence of a cutaneous erythematous diffuse maculopapular rash.^{64, 68}

It should be remembered that 90% of flucytosine is excreted by the kidneys and caution in patients with impaired renal function should be taken. However, it can be used safely in patients with renal insufficiency if the dosage is modified in accordance with the creatinine clearance. Finally, care must be taken when used in patients with bone marrow depression due to its potential toxicity to this location.⁶⁸

Cryptococcus neoformans es un hongo que Resumen: se ha asociado a meningitis en el hombre. Las manifestaciones más severas de la enfermedad se han correlacionado con la presencia de defectos de inmunidad celular del paciente. Sin embargo, un gran porciento de los pacientes que padecen de envolvimiento del sistema nervioso central no se les diagnostica defecto inmunológico alguno. Usualmente, el cuadro de meningitis es precedido por una infección pulmonar, que puede ser subclínica. El hongo puede diseminarse por vía hematógena a casi cualquier órgano, pero parece tener predilección por el sistema nervioso central. La meningitis que resulta se caracteriza por su evolución crónica o subaguda, haciéndose clínicamente aparente la enfermedad en un período que puede tardar semanas. El diagnóstico final se hace a base de los resultados de cultivos del líquido cefalorraquídeo y/o la detección inmunológica del antígeno de la cápsula del criptococo. La detección de anticuerpos en contra de la cápsula del criptococo es menos específica, y por sí sola de poca ayuda diagnóstica. El tratamiento de anfotericina B y flucitosina ha demostrado ser superior que el tratamiento con anfotericina B como agente único. La anfotericina B en combinación con flucitosina presenta menos fallos a terapia, recurrencias y efectos secundarios, aunque la mortalidad entre ambos regimenes utilizados parece ser similar.

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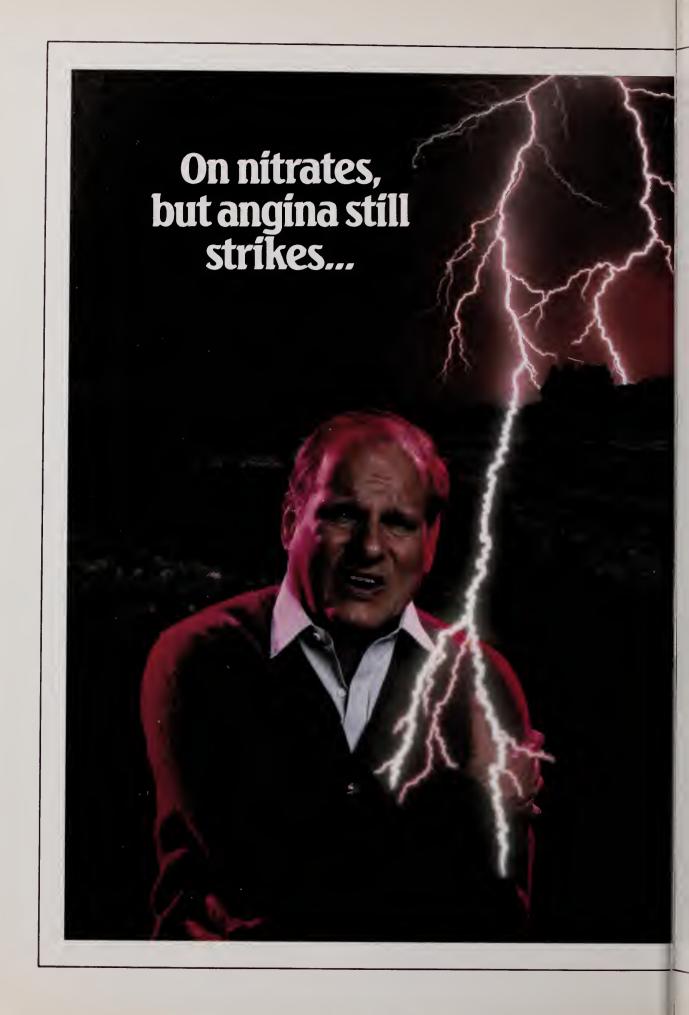
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ARTICULOS ESPECIALES

How to Treat Musculoskeletal Conditions — Practical Hints for The Internist*

Herman J. Flax, M.D., FACP**

Abstract: A number of practical measures to diagnose and treat common painful muscular syndromes have been presented. The physician must provide ample time for a complete history and look for signs characteristic of these conditions during the physical examination. Above all, the patient must thoroughly understand the nature of the disease and the necessary measures to control emotional as well as physical stress that produce the common principal musculoskeletal problems discussed in this paper.

will discuss some practical points to help in diagnosing and treating common, painful, musculoskeletal conditions. Using them, patients will never experience renal syndrome, ¹, ² a frequent complication in the elderly from therapy with nonsteroid antiinflammatory medications, nor central-nervous-system depression³, ⁴ that often follows use of ataraxic drugs in both young and old.

Topics include:

- 1. "Tale of the Tape" or Mechanical Low-back Syndrome.
- "Housewife's Dilemma" or Contracted Achilles' Tendons,
- 3. "Stress and the Secretary" or Suboccipital Neuralgia,
- 4. "Heart Attack" or Thoracic-outlet Syndrome,
- 5. "Seamstress Palsy" or Carpal-tunnel Syndrome, and,
- 6. "Roving Demon" or "Trigger" Points.

All these problems are readily diagnosed if time is taken to listen and examine patient carefully. The purpose of this paper is to emphasize these simple but fundamental concepts, stressed early in our medical training. I will always remember my Professor of Physical Diagnosis, Dr. Harry Walker, who, 47 years ago, told the class, "Listen to the patient; he is telling you his diagnosis." This phrase bears repeating despite all the exact, exciting and expensive laboratory studies we can order today.

Now, pain is the reason why patients usually consult me. With very few exceptions, the diagnoses are the same. Why is it, then, that symptoms persist despite acceptable medical prescription?

First, mechanical low-back pain, is a very common complaint, and the number of patients who have been made back cripples because of the diagnosis of "disk" and "arthritis" is astronomical. True, the patient may have a narrowed lumbar-disk space and degenerative arthritic changes because he/she is middle-aged, but, in most people, neither of these is the cause of low-back pain. Frequently, the etiology is unequal length of the lower extremities, producing muscle strain in the gluteal region and a "trigger" area radiating pain posteriorly down the thigh to the lower middle-calf. This is not due to a herniated lumbar disk. It can be diagnosed simply by measuring from the anterior superior iliac spine to the center of the lateral malleolus on both sides. If the difference is more than one centimeter, a heel-insert of the proper height should be placed in the shoe of the shorter side. With additional posture hints and exercises to stretch the hip muscles over a few weeks, your patient will bless you forever.

The next group with Contracted Achilles' Tendons is more common in young, short, working housewives. (Fig. 1) They come to the office smartly dressed in the latest fashion. Their low-back pain is present at all times. Most say it does not radiate, that it improves with bed rest only to return the next morning; and, they become progressively worse during the day, especially before retiring. The cause is not in the back but in the legs, because these young ladies have contracted heels cords due to wearing high heels all their lives. When they come

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home, they remove their shoes and put on slippers with flat heels that position the legs, and consequently, the center-of gravity backwards. They compensate by bending the hips and trunk forward putting strain on the gluteal and lumbar paravertebral muscles. Treatment is to stretch the Achilles' tendons and other posterior, lower-extremity muscles, especially, hip and hamstring muscles and strengthen the abdominal muscles. Flat heels should not be used in the evening or week-ends. At first, the heels of the shoes and slippers should be approximately the same height; and, as the Achilles' tendons respond to stretching, the heels should be lowered to $1^3/_4$ to 2 inches. Unless dorsiflexion of both feet, with the knees completely extended, easily reaches 90 degrees or more, flat heels should never be worn.

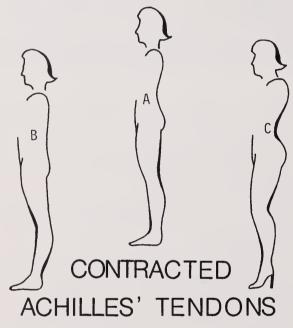


Figure 1. Contracted Achilles' Tendons. A-Normal Posture. B-Posture without heels. C-Posture with high heels.

Tension myositis of the shoulder-girdle and cervical muscles⁵, ⁶ is very common in both sexes but is especially evident in married women who work all day long and have to take care of a home, children and a non-loving husband in the evening. Very soon, muscles rebel, and patients develop different painful syndromes, including: headache, suboccipital neuralgia, stiff neck and shoulders, anterior chest pain, thoracic-outlet syndrome and weakness of the upper extremities.

These syndromes also develop in men who work under tension. Some of my patients are sedated to the point of hysteria, because the pain is real. Unless we take sufficient time to discuss all factors producing physical and emotional stresses, we will never treat these patients satisfactorily. This is why physiatrists have been dubbed inexpensive psychiatrists. In addition to listening, they place their hands on the patient. To treat a tension myositis, we must help solve the emotional as well as treat the physical manifestations.

Suboccipital Neuralgia is an excruciating headache that begins in the nucha and radiates across the occipitalparietal region to end supraorbitally. (Fig. 2) It is quite common in the secretary, who is overworked and overtired. It is caused by spasm of the tiny rotator and extensor muscles of the head found in the suboccipital muscular triangle and the cervical paravertebral muscles. The first cervical nerve and the second (Greater Occipital Nerve) pierce this area to become superficial nerves in the back of the head, and the Second extends forward to overlap the supraorbital nerve in the frontal parietal area. Treatment is to infiltrate the spastic muscles in the suboccipital region with a local anesthesia, Lidocaine Hydrochloride, 3-5 mls. of a one percent solution. Most important: discuss etiological factors with the patient, modify postural habits at work and at home and speak with the husband about cooperating and providing tender-loving care.

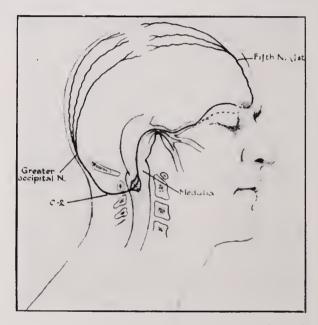


Figure 2. Path of Greater Occipital Nerve connecting with Supraorbital Nerve, referred pain of Suboccipital Neuralgia.

The pain accompanying a *Thoracic-outlet Syndrome* runs down the ulnar side of the forearm and hand, similar to an attack of angina pectoris and coronary thrombosis. Also, both have precordial radiation.

The diagnosis is made by performing an Adson's maneuver that compress the subclavian artery and diminishes the radial pulse. There are several variations of this test, one of which is the Flax modification: the patient lies on his back with the involved upper extremily at 90° abduction and the forearm flexed at 90 degrees. The physician holds this position by grasping the patient's elbow with one hand. With the other, palpate the radial pulse and passively rotate the arm through full external rotation. The pulse weakens or disappears if there is subclavian-artery compression, usually by a tight anterior scalenus muscle. Still with the arm rotated, the patient is asked to take a deep breath and hold it, which usually diminishes the pulse more. Finally, without

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expelling the air, the patient is requested to turn the head to the opposite side, or the head is passively rotated with the hand that held the elbow. The radial pulse will diminish even more or disappear. The same complete maneuver is done on the opposite side, and the pulse should not disappear nor even diminish unless some pathology is present.

Treatment is directed to improve the poor posture of the head, neck and chest with shoulder-girdle and thoracic-outlet exercises. If the patient exercises faithfully and gets rid of emotional stress, there is no need for

surgery.

There is nothing tricky about a Carpal-tunnel Syndrome if you keep it in mind to explain the pain, burning and weakness of the hands. It is common in people who work continuously with their hands. In many young women, there is a periodic aggravation of symptoms with premenstrual fluid retention. Long before thenar muscle atrophy, the electromyographic examination shows prolongation of sensory-nerve conduction latency. Treatment is modification of the job and early use of an anatomical wrist splint to prevent constant motion. Retention of fluid is treated using diuretics. If this fails, try injection of local anesthetic solution with corticosteroid into the carpal canal, not the median nerve; and, finally, surgery to relieve median-nerve compression by cutting the transverse carpal ligament

and freeing the nerve.

"Trigger Points," (Fig. 3) produce a myriad of distal pain syndromes when a particular sensitive area is stimulated. The referred pain usually follows a dermatomic distribution but not necessarily so. Although "triggers" are more common in muscles and are myofascial in location, there are also referred pain syndromes from the internal organs: i.e., ulnar distribution from a coronary thrombosis, to the right shoulder from gall bladder disease, and the characteristic flank to inguinal radiation of a renal colic.

The real reason for the formation of "triggers" is not known. In my opinion, trauma, gross or minute, produces muscle-fiber tears that heal with scars, a myofasciitis. This tissue is not as elastic as the original muscle, is subject to repeated minute tears as we work and play and becomes a focus of irritation. A vertebral osteophyte stimulates an axon producing continuous, although imperceptible, muscular contractions. Metabolic, vascular and neurophysiological causes have been advocated. Anxiety, whatever the reason, produces muscle spasm, a tension myositis.

A "trigger point," whatever the cause, becomes a focus of irritation and sets up a reflex arc that is characterized by distal pain, muscle spasm, pain. This condition is treated by locating the "trigger point" and injecting it with local anesthesia. It is interesting to note that many of

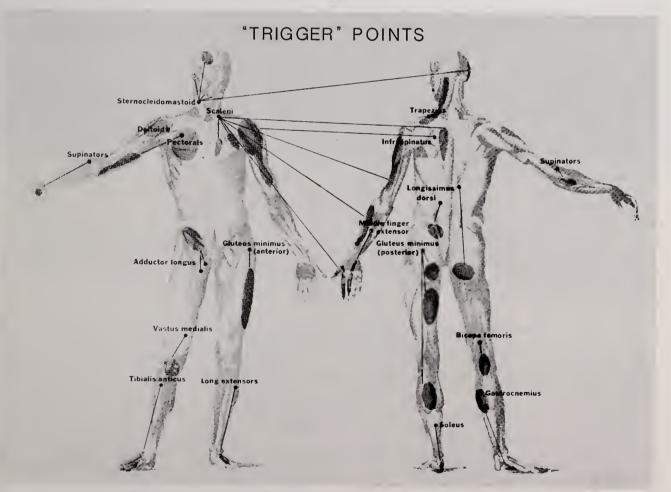


Figure 3. Trigger areas (Points) and their patterns of referred pain (Shaded). Used with permission of *Pfizer Spectrum*. JAMA 1953; 152:7.

the "trigger points" and acupuncture points have similar locations. Perhaps, it is the needle and not the solution that breaks up the vicious circle.

But, first, the "trigger point" must be found, and the symptoms reproduced by pressure on this spot. I call your attention to the trapezius "trigger" with the pattern of referred pain to the neck and the occiput, the gluteus minimus "trigger" with a sciatic-like distribution, except the referred pain does not go into the foot, and the pectoral "trigger" with spread over the precordium and internal surface of the arm. These pain syndromes can easily be confused with more serious medical diseases requiring more heroic treatment than an injection of local anesthesia, posture hints, muscle stretching and strengthening exercises and an explanation of the nature of the problem.

Conclusion

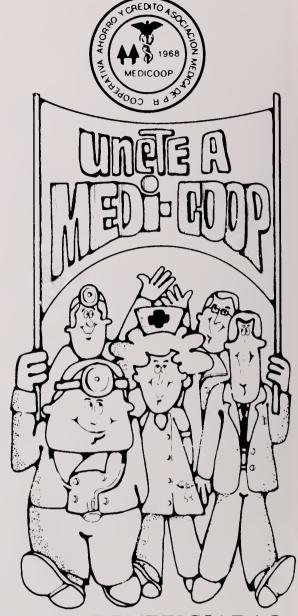
A number of practical measures, useful in diagnosing and treating neuromuscular pain syndromes, have been discussed. They are common complaints, and lasting relief cannot be achieved by prescribing the vast numbers of nonsteroid antiinflammatory or ataraxic drugs flooding the medical market today. This is especially true in geriatric patients, in whom renal and CNS syndromes are frequent, life-threatening complications from these medications. Emotional problems and repeated physical stress on the job and at home are important etiological factors.

Therefore, we must take sufficient time to listen to the patient and carefully search for signs of these syndromes. Otherwise, we will not make the correct diagnosis despite extensive and expensive diagnostic procedures, and the patient will continue to suffer not withstanding prescription of high-priced medication.

Resumen: Se presentan algunas medidas útiles para diagnosticar y tratar algunos síndromes musculares corrientes y dolorosos. Es menester que el médico tome tiempo suficiente para conseguir un historial amplio y practicar un examen físico cuidadoso para encontrar las señales propias de estas condiciones. Sobre todo, el paciente debe comprender completamente la naturaleza de la enfermedad y las medidas necesarias para controlar el "stress", tanto emocional como físico, razón principal de los problemas musculoesqueletales comunes presentados en este artículo.

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2. In front of a mirror.

Observe breasts. Arms at sides. Raise arms high overhead. Any change in nipples, contours, swelling, dimpling of skin? Palms on hips: press down firmly to flex chest muscles.



3. Lying down.

Pillow under right shoulder, right hand behind head. Left hand fingers flat, press gently in small circular motions starting at 12 o'clock. Make about three circles moving closer to and including nipple. Repeat on left.



Presentación de Casos

Hypokalemic Periodic Paralysis: A Rarely Considered Diagnosis in the Pediatric Patient

Alicia Fernández-Seín, M.D., F.A.A.P. Marisel Vázquez, M.D.

Abstract: A 14-year-old Puerto Rico male who had recurrent episodes of generalized weakness and flaccid paralysis was admitted with hypokalemia (1.3 meq/1). Paralysis resolved with intravenous correction of serum potassium. Except for one recurrence, patient has remained asymptomatic on diet potassium supplementation. Hypokalemic periodic paralysis is a rare condition whose onset is usually at adolescence. It is caused by unstable balance of serum potassium levels. Low-carbohydrate diet, potassium supplementation, spironolactone and acetazolamide have been used successfully in stabilizing serum potassium levels and decreasing frequency of paralytic attacks in these patients.

Hypokalemic familial periodic paralysis is the most frequent of the four described syndromes of periodic paralysis. It is, however, a rare disorder whose basic defect is unknown. Although attacks usually start at puberty as episodes of weakness or paralysis when the patient wakes up, it is seldom discussed in the pediatric literature. The disease is inherited as an autosomal dominant trait but sporadic cases have been reported. In this article we will present one of these sporadic cases, the first to be reported in an adolescent Puerto Rican male.

Case Report

A 14-year-old male patient was referred to the Emergency Room of the University Pediatric Hospital because he had been unable to move his arms and legs since that morning. For the previous two months he had been having early morning episodes of mild weakness which improved gradually during the next few hours after awakening. He had approximately two such episodes per month. On the day of admission the weakness progressed to generalized paralysis and did not improve as on previous occasions. There was no history of trauma, preceding viral illness or family history of paralysis.

Physical examination was unremarkable except for flaccid quadriparesis with involvement of neck muscles, urinary retention and abdominal respirations. The patient was admitted to the Pediatric Intensive Care Unit because of probable respiratory failure. Diagnostic possibilities entertained included ascending polyneuritis and myasthenia gravis. Results of examination of cerebrospinal fluid, sedimentation rate and muscle enzymes were normal except for a mild increase in creatine phosphokinase value (82 units). A tensilon test was performed without response. Serum electrolytes were all within normal limits except for a potassium level of 1.3 mEq/1. There was evidence of flat T waves, prologed QRS and QU intervals on the electrocardiogram (ECG). (Fig. 1) In view of these findings, the diagnosis of hypokalemic periodic paralysis was strongly considered. Therapy with intravenous fluids using 0.45 normal saline solution in 5% glucose in water with added potassium chloride at 40 mEq/1 was administered. This resulted in improvement within a few hours with correction of serum potassium levels to 5 mEq/1. Thereafter, therapy was started with low-potassium diet and spironolactone 25 mg p.o. b.i.d. An electromyogram, performed after correction of hypokalemia, was normal. The patient was discharged home two days after admission without muscular deficit.

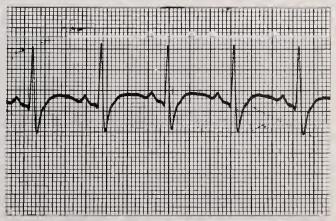


Figure 1. ECG upon first admission reveals widening of the QRS complex, flattening of the T wave and a prolonged QT interval with a U

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In a follow-up visit, spironolactone was discontinued and potassium supplement was given as potassium chloride 20 mEq p.o. t.i.d. This regimen maintained adequate serum potassium levels.

Two months after his first admission the patient was admitted again to the Pediatric Intensive Care Unit with another episode of generalized paralysis. According to the patient, he did not receive his potassium supplement the day before, had indulged in excessive exercise, and had had a large carbohydrate diet. On admission, ECG disclosed flat T and U waves. (Fig. 2a, 2b) The patient responded to intravenous 0.45 normal saline solution in 5% dextrose in water with 60 mEq/1 of potassium chloride. Serum potassium level during this episode was 1.6 mEq/1; after correction, it returned to 4.2 mEq/1. Physical examination after the episode was normal except for persistent arreflexia.

The patient was discharged home two days after admission on a low-carbohydrate, low-salt diet and potassium chloride 20 mEq p.o. t.i.d. He has been followed for the last year at the Continuity Care Clinics without any recurrences of paralysis, and with normal serum potassium and ECG. (Fig. 3)

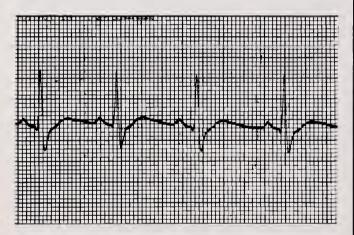


Figure 2A. ECG on second admission shows prolonged QRS, Flattening of T waves, and subtle $\,U\,$ waves.

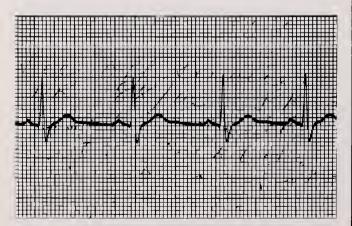


Figure 2B. ECG during potassium therapy where U waves are present QU interval is prolonged in contrast with a normal QT interval.

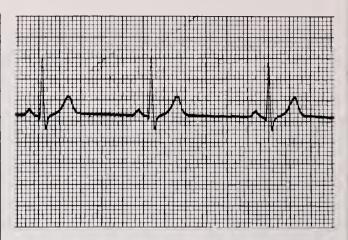


Figure 3. Follow up ECG with normal serum potassium. The QRS and QT intervals are normal. No U wave present.

Note: ECG derivation is LEAD II and calibration is 1 mV = 1 mm

Comment

Hypokalemic periodic paralysis, a rare disorder, is the most common of four described clinical forms of periodic paralysis: (1) hypokalemic periodic paralysis, (2) hyperthyroidism with periodic paralysis, (3) congenital paramyotonia of the tongue and hypothenar muscles and (4) adynamia episodica hereditaria, (associated with hypokalemia). Musgrave was the first to describe this disorder in 1717.1 It is inherited as an autosomal dominant trait but sporadic cases have been reported in 5% of cases.² Males are more frequently and severely affected than females.3 Patients are completely normal except during episodes of weakness or paralysis associated with low serum potassium levels.2, 4, 5 Onset is usually at puberty and attacks decrease in frequency and severity with advancing age. Episodes may begin at night and the patient wakes up unable to get out of bed due to generalized weakness. Proximal muscles are the most commonly affected.^{1, 2} Facial, pharyngeal, thoracic and diaphragmatic muscles become involved in the most severe cases. Death secondary to respiratory paralysis has been reported in 10% of affected patients.² Attacks may last for six to twenty four hours. 1, 6 Serum potassium values decrease below 3.5 m Eq/1 while those of intracellular potassium rise. Electromyogram shows electrical silence during the hypokalemic episodes.^{1, 2} Between attacks all findings return to normal. In several cases, some degree of weakness has been reported after termination of the attack, followed by slowly progressive myopathic weakness during middle and late adult life.²

Although the etiology of periodic paralysis is still obscure, there is considerable agreement among investigators about the pathophysiological mechanism. The periodic paralyses appear to be diseases in which serum potassium is unstable, diverse stimuli trigger attacks, and there are increased potassium fluxes between serum and cells. 1, 7, 8 In hypokalemic familial periodic paralysis there is a reduction of serum or extracellular K+ during the attack, increasing intracellular K+ accordingly. However, there have been cases reported in which there is

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no direct relationship between serum potassium levels and muscle weakness.⁸ Most cases demonstrate predictable changes in serum K+ during attacks, but certain patients may undergo paralytic episodes even with normal serum potassium levels.¹

Various etiologies have been considered as possible explanations for the periodic paralysis. Some authors suggest an abnormality of muscle cell carbohydrate metabolism because muscle biopsy shows vacuoles that seem to be filled with glycogen.², ⁹ Conn in 1957 suggested that the primary defect was an intermittent secretion of ACTH or mineralocorticoids.^{1, 4} Others have suggested cellular organelle defects and a primary defect in the depolarization of muscle membranes.¹⁰ Pearson described vacuoles appearing in the muscle specimens of biopsies taken both during the ictal and post-ictal states.2, 11 He also found dilated endoplasmic reticulum in these specimens. There is long-term damage to muscle with evidence of vacuolization and segmental necrosis which leads to the eventual loss of muscle function. This may lead to permanent mild to moderate weakness in late adulthood. These changes occur primarily at the hip girdle and proximal muscles.

Our patient appeared to be the first in his family to be affected. He presented a progressively ascending weakness with involvement of intercostal muscles and initially ascend-polyneuritis was suspected. But with the history of previous mild episodes of morning weakness that resolved spontaneously and the finding of a low serum potassium we suspected hypokalemic periodic paralysis. We did not perform a challenge test with insulin and glucose on his first admission but had a confirmation of our diagnosis with the reappearance of symptoms on his next admission when he discontinued the potassium supplementation.

The second episode of paralysis was probably precipitated by a large carbohydrate meal and exercise, as described in this condition. There may be other factors that can precipitate hypokalemia; cold, alcohol intake, sodium loading and drugs such as insulin and epinephrine.^{1, 2, 4, 12} Paralysis can be experimentally induced with insulin and dextrose. Muscle weakness is triggered by a massive uptake of potassium into the muscle cells and a subsequent lowering of serum K+.

The electrocardiogram changes that our patient exhibited during the hypokalemic episodes disappeared upon correction of serum potassium level. It has been reported that ECG signs of hypokalemia are more pronounced in patients with periodic paralysis than in normal persons with the same level of hypokalemia. Therefore, careful ECG monitoring can detect early potassium changes.

The acute management of this condition is the intravenous administration of potassium. Long-term management consists of a low-carbohydrate diet and potassium supplements. Spironolactone, a potassium-sparing diurectic, has been used in cases that do not respond to previous measures. Some studies reveal that acetazolamide is the drug of choice for prevention of attacks.⁷, ¹³

According to Vrooen et al the main finding relevant to the effect of acetazolamide on periodic paralysis is that of stabilizing serum K+ against the fall that glucose and insulin may provoke. Acetazolamide works through induction of acidosis. The acidotic state opposes the tendency of K+ to leave serum for intracellular sites in normals and in patients with this disease. Further investigations by Johnsen have shown significant lower glucose and insulin levels in patients treated with acetazolamide. This might be due to a reduced absorption and deposition of glucose in muscles. This would further improve the prophylactic action of acetazolamine. The recommended dosage of acetazolamide is 250 mg.p.o. two or four times a day, as necessary to keep adequate potassium values.

Our patient has been kept asymptomatic with diet and potassium supplements (20 mEq t.i.d.). He has experienced only two episodes of paralysis in one year after diagnosis. The second episode was precipitated by a combination of factors: large carbohydrate intake, exercise, and a period of twenty four hours without potassium supplementation. We plan to add acetazolamide if he develops further attacks while on the present regime.

To date, he has not exhibited residual weakness. However, this is a late complication in this disease and long-term follow-up is mandatory.

In conclusion, although hypokalemic familial periodic paralysis is a rare disease, its onset is usually in adolescence. The pediatrician should be aware of this condition in order to establish its correct diagnosis and management, specially in situations where mild alteration in blood pH, insulin or glucose levels may occur (during anesthesia, exercise, hyperventilation, stress, etc.) and which may elicit a paralytic attack.

Resumen: Un paciente varón de 14 años de edad es hopitalizado con episodios repetidos de debilidad generalizada e hipocalemia (1.3 meq/L). La parálisis desaparece al corregir el potasio con líquidos endovenosos. El paciente permaneció asintomático, excepto por una recaída, mediante dieta y suplementación oral de potasio. La parálisis periódica hipocalémica es una condición rara cuya primera manifestación ocurre en la adolescencia. Es causada por desequilibrios en los niveles de potasio sérico. Las dietas bajas en carbohidratos, suplementos de potasio, espironolactona y acetazolamida se han usado como agentes para estabilizar el potasio sérico y disminuir la frecuencia de los ataques paralíticos.

Acknowledgements

The authors wish to thank Dr. Juan Villafañe for the interpretation of the ECG of this patient; Dr. José Sifontes and Dr. José M. García-Castro for the critical review of the manuscript. The secretarial assistance of Ms Vivian Rodríguez is greatfully acknowledged.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C.* Angel Espinosa López, M.D.

HCL es una niña de 3 años de edad con un historial médico negativo hasta hace un año. Durante un episodio de bronquiolitis y taquicardia persistente se hizo una radiografía de tórax que reveló cardiomegalia marcada. Se digitalizó con buena respuesta clínica pero durante el período de seguimiento apareció un soplo sistólico en el apex. El mismo fue progresivamente aumentando en intensidad y duración y el electrocardiograma (ECG) era compatible con hipertrofia ventricular izquierda. La cardiomegalia con congestión venosa persistía en sus radiografías por lo que se hospitalizó para estudios diagnósticos invasivos.

El examen físico demostró una niña sin cianosis, con crecimiento y desarrollo adecuados para su edad. El ritmo cardíaco era de 120/min., regular, con tonos cardíacos discretamente disminuidos. El precordio era activo, con PMI en el 5° espacio intercostal izquierdo cerca de la línea axilar anterior. El soplo era holosistólico, grado 3/6, con tonalidad en chorro de vapor ("blowing") y se apreciaba mejor en el apex con irradiación a la axila y espalda. El timbre del S_1 estaba disminuido, el S_2 estaba normal y se apreciaba un tercer sonido (S_3) cerca del apex. No había componente diastólico, los pulmones estaban claros y los pulsos periféricos buenos pero se palpaba el hígado 3cm, bajo el borde costal derecho.

La Hb. era de 12gm., el ECG demostraba hipertrofia ventricular izquierda y agrandamiento atrial izquierdo sin cambios significativos en el segmento ST ni en la onda T. En la radiografía de tórax persistía la cardiomegalia marcada con congestión pulmonar venosa.

En la figura 1 se enseña el ventriculograma izquierdo de la niña.

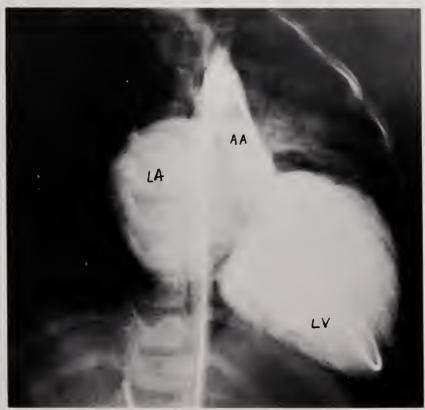


Figura 1. Ventriculograma izquierdo por vía retrógrada con el paciente en posición oblicua anterior derecha a 30°.

CUAL ES SU DIAGNOSTICO?

- Miocardiopatía Idiopática Congestiva
- Insuficiencia Mitral Severa

La miocardiopatía idiopática congestiva (MIC) es una enfermedad primaria del miocardio que no es consecuencia de enfermedad valvular, pulmonar, infiltrativa, coronaria ni hipertensiva. Se caracteriza por dilatación de las cavidades ventriculares, aumento en la masa miocárdica y ausencia de células inflamatorias en el miocardio. A pesar de este aumento en la masa miocárdica, el grosor de la pared ventricular izquierda y del septo interventricular no suele sobrepasar los valores normales de acuerdo a la edad del paciente como sucede en la miocardiopatía hipertrófica obstructiva.

La dilatación ventricular izquierda da lugar a una contracción ventricular pobre, lo cual ocasiona una fracción de eyección ventricular reducida y por consiguiente un aumento en el volumen sistólico-final del ventrículo izquierdo y dilatación atrial izquierda.² Se dice que el tamaño de la cavidad izquierda dilatada es proporcional a la severidad y duración de la insuficiencia cardíaca.

El aumento en el volumen ventricular izquierdo al final de la sístole además de las consecuencias hemodinámicas ya mencionadas tiende a ocasionar una estasis sanguínea en la parte apical de las cavidades cardíacas lo cual resulta frecuentemente en trombosis intracavitarias. Debido a la estasis sanguínea ocasionada por el pobre vaciamiento atrial también pueden ocurrir formaciones trombóticas en los apéndices auriculares. Estos trombos intracardíacos pueden fácilmente dar lugar a procesos embólicos sistémicos y pulmonares. En autopsias de pacientes con MIC se ha informado la presencia de trombos en la cavidad ventricular izquierda en un 75% de los casos.¹

Aunque en la MIC puede apreciarse histológicamente fibrosis miocárdica en grado variable, la presencia de fibrosis macroscópica en la pared ventricular izquierda solo está presente en menos de 25% de los casos. Cuando la fibrosis es visible por lo regular está limitada al músculo papilar y sub-endocardio, de manera que la pobre contractilidad del miocardio en la MIC no puede ser atribuida solamente a este proceso fibrótico.

La causa de la insuficiencia mitral en estos pacientes parece ser debida a disfunción de los músculos papilares, pues el anillo mitral y tricuspídeo de estos pacientes suele estar solo levemente dilatado. Casi nunca esta dilatación anular sobrepasa un 25% del tamaño normal. Tampoco suelen estar engrosadas las valvas mitrales en los pacientes con MIC, si lo están puede ser secundario a la regurgitación en sí, sin que este engrosamiento sea el causante de la insuficiencia valvular.

Los hallazgos clínicos presentes en nuestro paciente (disminución de S₁, soplo de insuficiencia mitral, S₃, hepatomegalia, etc.), junto con los radiológicos (cardiomegalia y congestión venosa) y electrocardiográficos (hipertrofia ventricular izquierda, agrandamiento atrial izquierdo y cambios en ST) son los usuales en los pacientes con MIC e insuficiencia mitral significativa.

La figura l representa el ventriculograma izquierdo de nuestro paciente en posición oblicua anterior derecha a 30º. Se demuestra la dilatación de la cavidad ventricular izquierda, el agrandamiento del atrio izquierdo por la insuficiencia mitral y el engrosamiento de las valvas mitrales. Angiográficamente estos hallazgos son compatibles con disfunción ventricular izquierda marcada e insuficiencia mitral severa.

La regurgitación valvular puede visualizarse angiocardiográficamente observando la opacificación del compartimiento proximal a la válvula incompetente luego de la inyección de material de contraste en el compartimiento distal.⁵ La determinación de la severidad de la regurgitación está basada en:

- el grado de opacificación del compartimiento proximal (en nuestro caso el atrio izquierdo) en términos de area opacificada y densidad de opacificación.
- el tiempo que tarda en "aclarar" el contraste en este compartimiento proximal.

Para la evaluación angiográfica semicuantitativa de la regurgitación mitral se siguen los criterios propuestos por Sellers en 1964.⁶ De acuerdo a los mismos nuestro paciente tendría una insuficiencia mitral grado 3 (el máximo es grado 4) donde: no se ve el chorro o "jet" de contraste; la opacificación atrial izquierda es tan intensa como la del ventrículo izquierdo y de la aorta en las últimas radiografías de la serie; y el atrio izquierdo está considerablemente agrandado.

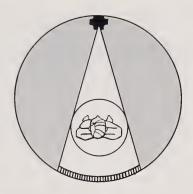
El tratamiento de la MIC ha consistido tradicionalmente en el uso de digoxin y diuréticos. Recientemente se han incorporado al armamentario terapéutico de la MIC algunos agentes vasodilatadores con resultados de efectividad variable.

Es difícil poder predecir el curso clínico y pronóstico de la MIC, sin embargo sabemos que una vez se instaura la insuficiencia cardíaca esta es de carácter progresivo y desenlace tarde o temprano fatal.

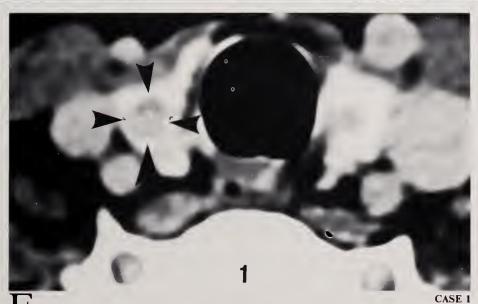
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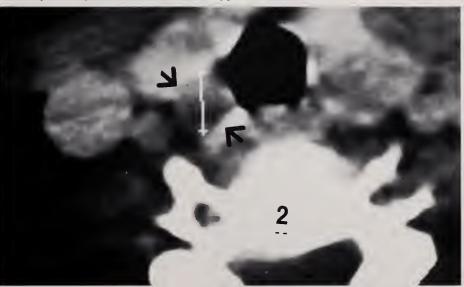




Heriberto Pagán Sáez, M.D.



Porty three years old female with hypercalcemia.



 $\mathbf{F}_{ ext{orty seven years old female with hypercalcemia.}}$

CASE 2

WHAT IS YOUR DIAGNOSIS?

^{*}Director, Department of Radiological Sciences, University of Puerto Rico, School of Medicine

DIAGNOSIS: Parathyroid Adenoma

These cases were proven at surgery. Case I shows an intrathyroid localization while case 2 presents the usual posteromedial locus as would be expected anatomically. These two cases prove the value of "thyroid computerized tomography" as the initial diagnostic procedure in cases highly suspicious of hyperparathyroidism. Prior to the advent of high resolution third generation CT scanners the diagnostic work up for parathyroid adenoma included high risk vascular procedures and many times "blind neck and mediastinal surgical exploration".

In our experience of five cases, four were correctly localized and one case wrongly diagnosed because of technical problems. The fact that four of five adenomata were easily reached surgically and successfully extirpated based on the CT findings speaks very well of the very low risk diagnostic procedure. We firmly beleive that no patient suspected of parathyroid adenoma should reach the operating room without the benefit of a thin slice (5 mm or preferably 1-2 mm) thyroid CT with contrast.

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Curet, José O., MD - Universidad de Puerto Rico, 1975, Obstetricia y Ginecología. Ejerce en Hato Rey.

Heyliger Sánchez, Eduardo, MD - Universidad de Madrid, 1966, Obstetricia y Ginecología. Ejerce en Santurce.

Padilla Ramírez, Hemán F., MD - Universidad de Maryland, 1963, Nefrología y Medicina Interna. Ejerce en San Juan.

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Vargas de Padilla, Miriam S., MD - Universidad de Puerto Rico, 1971, Medicina Física y Rehabilitación. Ejerce en San Juan.

ACTIVOS NO RESIDENTES

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Rivera Vélez, Jaime Hernán, MD - Universidad de Harvard, 1976, Pediatría. Ejerce en Texas, EE UU.

ACTIVO ESPECIAL

García Dorta, Linda Mabel, MD - Universidad Central del Caribe, Cayey, 1981. Ejerce en Río Piedras.

INTERNOS-RESIDENTES

Garib García, Lidia, MD - Universidad de Puerto Rico, 1982, Medicina Física y Rehabilitación, San Juan.

González Muñiz, Francelis, MD - Universidad Nacional Pedro Henriquez Ureña, República Dominicana, 1981, Pediatría. Ponce.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que

pudiera ser de interés general para la profesión médica. Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El articulo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: titulo, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Árticulos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos. Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias

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Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse sola mente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

omenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially).

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures
Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

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These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should be abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

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If there are more than 7 authors list only 3 and add et al.

For books when the authors of the cited chapter is at the same time the editor. Surname and initials of author(s), title, edition, city, publishing house, year

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Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 789

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Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five

*The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

New studies uncover the potassium effects of beta-2 blockade

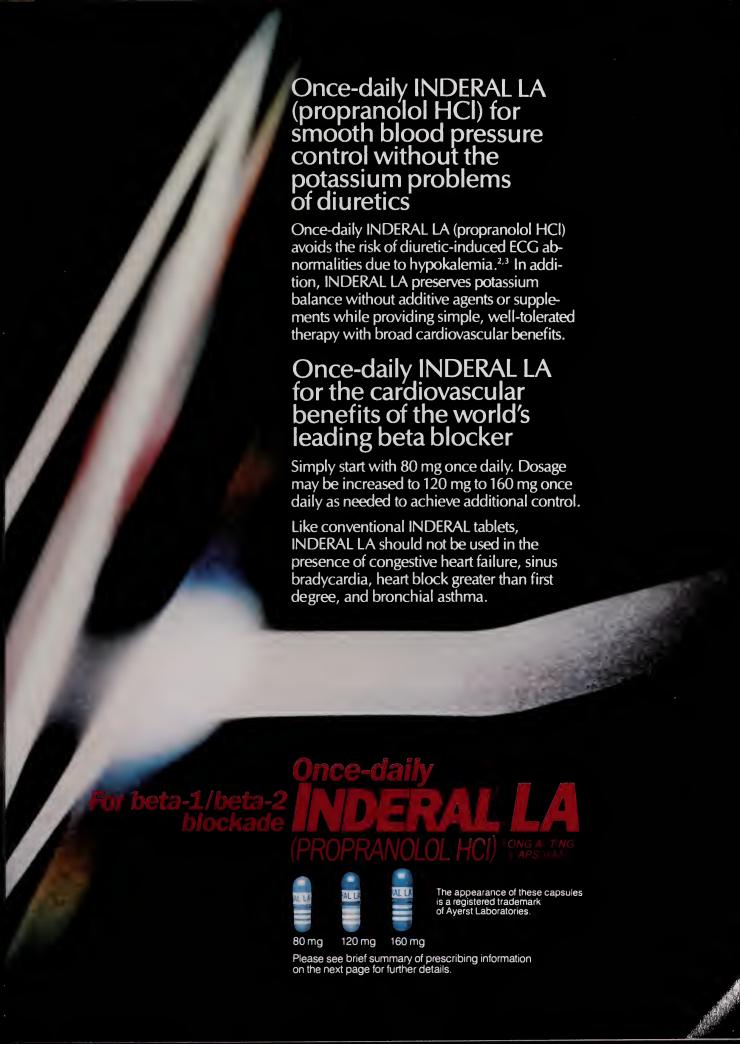
Clinical pharmacology data from The New England Journal of Medicine:

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."

Evidence I that all beta blockers are not created equal.

Right from the start in hypertension...





BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR) INDERAL* LA brand of propranolol hydrochloride (Long Acting Capsules) DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride inderal LA is available as 80 mg, 120 mg, and 160 mg capsules CLINICAL PHARMACOLOGY, INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor sitmulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCI at a controlled and predictable rate. Peak blood levels tollowing dosing with INDERAL LA occur at about 6 hours and the appaierint plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose in INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about livelve (12) hours then decline exponentially.

propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about liwelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect. INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period. The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of reini release by the kidneys, and (3) diminiotion of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated

the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache
efficacy of propranolol in the treatment of a migraine attack that has started has not been
ablished and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of

hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of

the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary. CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock. 2) sinus bradycardia and greater than first degree block. 3) bronchial asthma. 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart suited.

muscle
IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers
can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart
failure, the patient should be digitalized and/or treated with diuretics, and the response
observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given proprianolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA
BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors
MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy
prior to major surgery is controversial. It should be noted, however, that the impaired ability of
the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and exignal procedures.

sia and surgical procedures







The appearance of these capsules is a registered trademark of Ayerst Laboratories

INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta blockers againsts and its effects can be reversed by administration of such agents, cobutamine or isoproterenol. However, such patients may be subject to protracted se hypotension. Difficulty in starting and maintaining the heartbeat has also been reported

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the

DIABELES AND HYPOGLYCEMIA Beta-agreering blockage may prevent the pearance of certain premonitory signs and symptoms (pulse rate and pressure changes acute hypoglycema in labile insulin-dependent diabetes. In these patients, it may be indifficult to adjust the dosage of insulin. THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyrod. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of sympto flyperthyroidism, including thyroid storm. Propranolol does not distort thyroid functionals. IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have better the which after propranolol, the tachyradida was replaced by a severe braderic.

reported in which, after propranoiol, the tachycardia was replaced by a severe bradyca requiring a demand pacemaker. In one case this resulted after an initial dose of 5

PRECAUTIONS. General Propranolol should be used with caution in patients with impa hepatic or renal function INDERAL (propranolol HCI) is not indicated for the treatmen hypertensive emergencies

nypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Pate
should be told that INDERAL may interfere with the glaucoma screening test. Withdrawall
lead to a return of increased intraocular pressure.

Climical Laboratory Tests. Elevated blood urea levels in patients with severe heart dise.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart diseelevated serum transaminase, alkaline phosphatase, lactate dehydrogenase
DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as it
pine should be closely observed if INDERAL is administered. The added catecholam
blocking action may produce an excessive reduction of resting sympathetic nervous act
which may result in hypotension, marked bradycardia vertigo, syncopal attacks, or orthos
hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals
been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studie
both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of signific
drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dis
levels. Reproductive studies in animals did not show any impairment of fertility that
attributable to the drug.

levels Reproductive studies in animals did not show any impairment of fertility that attributable to the drug
Pregnancy Pregnancy Category C INDERAL has been shown to be embryotox
animal studies at doses about 10 times greater than the maximum recommended humand
There are no adequate and well-controlled studies in pregnant women INDERAL shoursing Mohers. NDERAL is excetted in human milk. Caution should be exercised w
INDERAL is administered to a nursing woman
Pedratric Use Salety and effectiveness in children have not been established
ADVERSE REACTIONS. Most adverse effects have been mild and transient and trarely required the withdrawal of therapy
Cardiovascular bradycardia, congestive heart failure, intensification of AV block, the
tension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of
Raynaud type
Central Nervous System lightheadedness, mental depression manifested by insom
lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, vidisturbances, hallucinations, an acute reversible syndrome characterized by disorientation
time and place, short-term memory loss, emotional lability, slightly clouded sensorium. unistables, a factor eversible syntome characterized by distorter table time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics.
Gastrointestinal nausea vomiting epigastric distress, abdominal cramping, diarric consupation, mesenteric arterial thrombosis, ischemic colitis.
Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with ad and sore throat, laryngospasm and respiratory distress.
Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytope purpura Auto-Immune In extremely rare instances, systemic lupus erythematosus has b

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male in tence, and Peyronie's disease have been reported rarely Oculomucocutaneous reaction of the skin, serous membranes and conjunctivae reported for a beta blocker (practice).

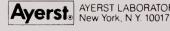
involving the skin, serous membranes and conjunctivae reported for a beta blocker (practivave not been associated with proprianolal DOSAGE AND ADMINISTRATION. INDERAL LA provides proprianolal hydrochloride sustained-release capsule for administration once daily. If patients are switched from INDE tablets to INDERAL LA capsules, care should be taken to assure that the desired therape effect is maintained. INDERAL LA should not be considered a simple mg for mg substitution. INDERAL LA has different kinetics and produces lower blood levels. Retirtation be necessary especially to maintain effectiveness at the end of the 24-hour dosing inte. HYPERTENSION—Dosage must be individualized. The usual initial dosage is 80 INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may increased to 120 mg once daily or higher until adequate blood pressure control is achier the usual minal dosage of mg may be required. The time needed for full hypertensive response to a given dosage wariable and may range from a few days to several weeks. ANGINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAl once daily, dosage should be gradually increased at three to seven day intervals until ophir response is obtained. Although individual patients may respond at any dosage level average optimum dosage appears to be 160 mg once daily In angina pectoris, the value safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few wellow.

(see WARNINGS)

MIGRAINE—Dosage must be individualized. The initial oral dose is 80 mg INDERAL once daily. The usual effective dose range is 160-240 mg once daily. The dosage maincreased gradually to achieve optimum migraine prophylaxis. If a satisfactory responses obtained within four to six weeks after reaching the maximum dose. INDERAL LA the should be discontinued. It may be advisable to withdraw the drug gradually over a periceparal weeks.

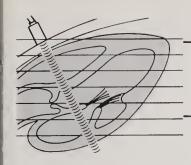
several weeks
HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are
Imited to permit adequate directions for use
REFERENCES

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ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., FACC*

This 81-year-old male admitted only to having chest pain. He could play 18 holes of golf. An electrocardiogram revealed left ventricular hypertrophy (LVH), left anterior hemiblock, Type IV, and Q waves in the right precordial leads. On an M-mode echocardiogram there was mitral annular calcification.

Doppler studies with and without simultaneous 2-D echocardiographic guidance, were performed and shown is figures 1-3.

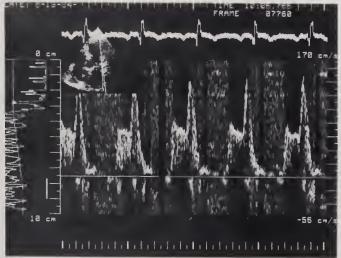
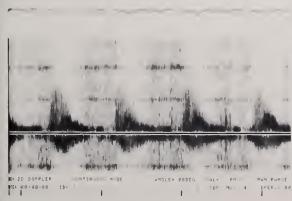


Figure 1



AND SHAPE SH

Figure 2 Fig

Figure 3

Charles D. Jonhson, MD, FACC, UPR School of Medicine, Section of Cardiology, Río Piedras, Puerto Rico 00936

- 1. What is the clinical diagnosis?
- 2. What are the Doppler diagnoses?
- 3. Explain the Doppler pulse pattern of Figure 1.

Answers

Calcific aortic stenosis (AS). Possible mitral stenosis. Concentric LVH. Decreased left ventricular (LV) compliance and elevated LV end-diastolic pressure (EDP).

Figure 1. Honeywell (Biosound Corp. Indianapolis, Ind) echocardiograph and 2.25 MHZ pulsed wave (PW) transducer. 2-D guidance. Apical 4-chamber view, with the sample volume (SV) placed in the LV inflow tract mitral velocity (see the left upper 2-D insert with cursor course). There is a very prominent "A" wave of 143 cm/Smaximal mitral velocity (V), as recently observed with decreased LV compliance and elevated LV EDP. Usually, the late peak due to atrial systole and contraction (A wave) is smaller than the early positive velocity (D wave) of rapid filling. The mean mitral velocity calculated by an Apple II Plus computer (Cupertino, CA) and disk from a prepared dedicated software program (Biodata, Davis, CA) was 41 cm/S. Mitral stenosis (MS) is a consideration, also. From the D and A wave velocities, the mitral valve gradients would be 2.6 and 8,2 mm Hg, respectively. The pressure halftime of Hatle (the time in mS it takes for the mitral pressure gradient to drop to one-half of its initial peak value) is hardly calculable in this trace:

$$V t^{1}/_{2}$$
 (diastolic half-value) = $\frac{V t_{0}}{V_{2}}$ (initial peak 80) = 57 cm/S,

reflecting a diastolic pressure half-time of 175 mS (normal 20-60 mS, mean 46 mS). In MS, it varies from 90-383 mS; mild 100 mS, moderate 200 mS, severe 300 mS.

Mitral valve area =
$$\frac{220}{\text{Pressure half-time}}$$
 = $\frac{220}{175}$ = 1.26 cm.²

In MS the A wave can be larger than the D wave, or augmented such as > 1 M/S.

Figures 2 and 3. Irex echograph (Ramsey, NJ). Continuous wave (CW), suprasternal notch, using an angled M-mode probe. There is a positive systolic aortic flow toward the transducer with has a peak V of 3.8 M/S, and a slightly disturbed, turbulent flow pattern with spectral dispersion. The calculated aortic valve gradient is about 58 mm Hg. Aortic blood flow cannot be calculated from a jet flow velocity trace. The aortic valve area may be computed as: Stroke volume $\overline{(0.88 \text{ x V}_2 \text{ x VET})} = 0.59 \text{ cm}^2$

using the pulmonary artery (PA) flow (4226 cc/min) to derive stroke volume (for semilunar valve area an uninvolved site must be chosen). The PA peak V was 72, the mean V was 18 cm/S and the PA diameter 2.2 cm.

The aortic valve was not crossed with the catheter during cardiac catheterization.

Discussion

Doppler echocardiography with 2-D echo guidance has proven extremely useful as a noninvasive, reliable method for determination of blood flows, pressure gradients and valve areas in humans.

The aortic valve stenosis gradient may be calculated applying a simplified version of the Bernoulli or energy balance equation:

$$P_2 = 4 V^2$$

$$(P_2-P_2, VG)$$

Where P_2 = distal pressure in mm Hg; pressure drop across the stenosis; the systolic pressure gradient (when P₁, the proximal pressure is normal-<1 M/S, or 4 mm Hg).

VG = valve gradient.

 V_2 = maximal distal velocity in M/S, in the stenotic jet.

The aortic valve area in AS may be determined by Doppler by applying a recently derived formula (Kosturakis et al):

$$A = \frac{\text{Stroke volume, cc}}{(0.88 \text{ x V}, \text{ x VET})}$$

Where $A = area in cm^2$.

0.88 is a constant for the aortic and pulmonic valves. $V_2 = \text{maximal velocity in cm/S}.$ VET = ventricular ejection time in second (S).

The peak systolic LV pressure in AS may be estimated, as the systolic blood pressure in the right arm plus the gradient.

The maximal flow velocity that can be detected (V max) for a given range (depth), emitted frequency (f_0) and beam-flow angle (0) is:

$$\frac{C}{(5.2 \times 10 \text{ --}5) \text{ R}_{\text{max}} \times \text{f}_0 \times \text{Cos } 0}$$

Where C = velocity of sound in tissue (1540 M/S). $R_{max} = maximum range.$

If V₂, or the jet velocity, or depth (range-velocity product) exceeds the Nyquist limit of pulsed (rangegated) Doppler, aliasing may occur. Aliasing causes a wraparound, decapitation or foldover of the maximal portion of the spectral pulse when: the sampling rate is too slow; the velocity is so great (>1.75-2.86 M/S) that the frequency of the returning sound waves is greater than the sampling rate. Alternatives consist of: 1) setting the zero velocity at the top or bottom of the recording paper, in order to cover the entire paper with the trace, 2) bringing the transducer closer to the target, 3) choosing a lower frequency transducer, 4) choosing high pulse rate frequency (PRF)- 5 M/S maximum- Doppler, 5) choosing CW Doppler with a capability of 6 M/S, 6) cutting and pasting the decapitated portion to the main base, and 7) changing the tranducer angle (then not known). Transducers of 2.25 - 3.5 MHZ may be unreliable at depths greater than 10-13 cm.

The normal LV inflow tract (mitral) peak velocity is typically < 1 M/S, actually 90 cm/S mean, range 60-130, in adults. The normal AAo peak flow velocity is 92-135, with a range of 72-170 cm/S.

The ascending aorta (AAo) may be interrogated from the suprasternal notch (preferred), the parasternal area, subcostally and apically (5-chamber, 2-chamber views).

As by Doppler echocardiography may manifest: 1) high pitched, uniform whistling from the stenotic jet, 2) increased peak velocity, such as 3.5-4 M/S, 3) spectral broadening, 4) increased time to peak velocity and prolongation of the ejection time - flow disturbances, jet. 5) outside the maximal velocity jet the signal is of lower pitch, containing many lower audio frequencies, produc-

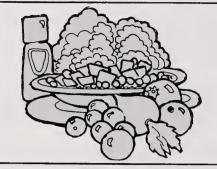
ing a less musical pure sound.

Combined PW and CW Doppler adds much to M-mode and 2-D echocardiography

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MEDICAL ASPECTS OF NUTRITION

Stress and Nutrition*

Deborah Kipp, Ph.D., R.D.**

tress" is a well-known and frequently used, but ill-defined, term. It has different meanings for different people, depending on life experiences and health history. An interaction between nutrition and stress to preserve health is known, although much work needs to be conducted before a thorough understanding of the relationship is gained.

Changes in metabolism and requirements for calories and protein have been thoroughly investigated during the past decade and clearly defined with illness and injury. ¹⁻⁴ Unfortunately, our current knowledge of vitamin and mineral requirements with these types of physical stress is inadequate to establish recommended levels for recovery.

Changes in the levels of circulating hormones have been demonstrated with emotional stress.^{5, 6} Knowledge, however, of the influence on metabolism and nutrient requirements is lacking.

In addition to physical and emotional stress, chemical stressors, such as tobacco, drugs and caffeine, may impact on nutritional requirements. Chemical stress factors will not be addressed at this time because they are beyond the scope of this paper.

Stress

Primary communication networks within the body to coordinate and integrate metabolism and the maintenance of homeostasis include the nervous, hormonal and vascular systems.⁷ The nervous system is the communication center, assessing the body's status relative to the environment (e.g., pain, thirst) and relays information for adjustment to these changes. The endocrine system rapidly adapts to maintain homeostasis of blood substrates, such as glucose, and regulates synthesis and degradation of substrates to meet energy needs. The vascular system delivers oxygen, transfers chemical messengers and eliminates toxins and metabolic end

products.

Stress, as described by Selye, is the "nonspecific response of the body to any demand made upon it." The nonspecific response refers to a generalized adaptation that must occur with stress to maintain physiologic equilibrium.

In addition to the nonspecific response, there are also unique, specific responses to various forms of stress. Depending on the stress, integrated changes in the nervous, endocrine and vascular systems occur to varying magnitudes and durations. ¹⁻⁴ These changes, in turn, will influence the metabolism and, consequently, the requirements of nutrients.

The physiological response to a stress is dependent on the type, magnitude and number of stresses imposed, genetic predisposition, frequency of exposure, age and other conditioning factors.⁸ Consequently, two individuals respond differently to the same stress.

It is generally assumed that a well-nourished individual is better able to cope with stress than a poorly-nourished individual. Whether this would be directly applicable to all forms of stress is not known.

Dubos suggested that almost any form of stress may upset nutritional balance. If an individual is marginally deficient in a nutrient, the stress may exacerbate the condition. Undernutrition is in itself a stress and the body undergoes adaptations to maintain equilibrium and adequate functional status when only a limited supply of nutrients is available. When additional stress is then superimposed on the already adapted state, the individual no longer has the same reserve capacity to adapt to the stress.

Nutrition and Physical Stress

Metabolic responses during injury and fever include increased stimulation of the nervous system and elevated secretion of many hormones, e.g., catecholamines and glucocorticoids. Since these physiologic changes influence nutrient metabolism, several characteristic nutrition-related consequences can occur. These include hypermetabolism, change in the production and utilization of glucose for energy, decreased protein economy and the loss of body weight and lean body mass.¹

^{*}Contemporary Nutrition Vol. 9 No. 7, July 1984. Reprinted with permission from General Mills Inc., Minneapolis, Minesota.

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Calorie and Protein Needs

An assessment of the change in metabolic rate in individuals with burns, trauma, surgery, fever, etc., is frequently obtained with gas exchange calorimetry. Hypermetabolism, measured as an increase in oxygen consumption above basal, reflects as increase in catecholamine-mediated activity in the body and a greater need for calories than in the pre-illness or injury state. For example, as the result of elective surgery, metabolic rate may increase by 5% to 10% and with severe trauma or infection, metabolic rate may increase by up to 55%. Fever, by itself, causes an increase of up to 13% in metabolic rate for each degree centrigrade of increase in body temperature.

With an increase in plasma catecholamine and glucocorticoid levels, there is increased liver production of glucose but decreased peripheral uptake of the glucose. This results in a tendency toward hyperglycemia. These dynamics of glucose metabolism generally relate to the severity of the illness or injury.^{1, 2, 4}

The hormonal changes accompanying physical stress also increase protein degradation, with amino acids becoming the primary energy source. The consequence of this is seen as an increase in the excretion of urine nitrogen. In addition, greater nitrogen losses would result from diarrhea and wound drainage. There is a close correlation between the magnitude of increase in the rate of nitrogen excretion and metabolic rate.⁴

Thus, protein and calorie needs are greater with illness and injury. For normal individuals, a calorie-to-nitrogen ratio of up to 350 calories for each 1 g nitrogen ingested will assure adquate calories to spare protein from being preferentially used for energy. With injury, the optimal ratio is between 100:1 to 200:1. Both caloric and nitrogen needs are increased until the repair process is completed, with needs decreasing as the hormonal levels return to normal.

Vitamins and Minerals

There is inadequate data available from which to establish increased requirements for vitamins and minerals. If there were a greater need for any vitamin or mineral with injury, it could be the result of inadequate absorption or utilization, or increased metabolism or excretion of the nutrient. To For example, decreases in intracellular ions, such as potassium, result from the loss of lean body mass.

Deficiencies in vitamins or minerals could be precipitated by inadequate ingestion coupled with greater requirements. Deficiencies in vitamin C and zinc are associated with poor wound healing. 11, 12 The requirements for thiamin and riboflavin, which are based on caloric intake, would increase as the need for energy increased. 12 It is not known whether an additional increment of intake above this level is needed.

Food Intake

Unfortunately, food intake often tends to be inadequate to meet nutrient requirements during the acute phases of physical stress. This results from depressed intake, nausea and vomiting or food being withheld for surgery or diagnostic tests. Increased nutrient needs combined with decreased food intake can impair and prolong the recovery process. Preexisting malnutrition or development of the malnourished state because nutrient needs are not met is a confounding factor in the recovery process that is associated with delayed wound healing, impaired immune function and increased morbidity and mortality.^{1, 4}

Temperature Stress

Other physical stresses, such as changes in ambient temperature, also may influence nutrient requirements. Humans generally control heat loss and gain by vasomotor regulation of skin blood flow and sweat rate without major alteration in the metabolic rate. However, when the environmental temperature drops below about 20°C, the sympathetic nervous system is stimulated. This accelerates heat production to maintain body temperature. The amount of heat produced in the body is regulated according to the needs of the body, as influenced by the environmental temperature. Nonshivering mechanisms are involved first; then, as the environmental temperature falls, shivering will occur.

Heat production causes a rise in basal metabolic rate and, therefore, an increase in caloric needs. There are no definitive studies demonstrating greater need for protein, vitamins or minerals with cold stress. On the other hand, decreased adaptation to cold, as measured by the ability of the body to regulate body temperature, has been reported with deficiencies of some nutrients, such as iron.¹³

There is not general agreement as to whether a hot environment also alters metabolic rate and, thus, energy needs.¹⁴ Nevertheless, if the body's capacity to dissipate heat through sweating is exceeded, the body core temperature will rise. This will elevate metabolic rate, as seen with fever. In addition, profuse sweating results in water, sodium and nitrogen losses. Of less magnitude are losses in iron, calcium and magnesium.¹

Nutrition and Emotional Stress

Since most hormones effect metabolism, stress could theoretically alter nutrient requirements when hormonal levels are altered.⁷ The difficulty in conducting carefully controlled clinical studies to document this, however, can be well-apreciated. Quantifying and comparing the impact of stresses of life is problematic. One approach to quantification has been to identify the correlation of life's stresses with development of illness, with the impact of the stressful event measured by the readjustment required when the event occurs.15 The contribution of a stressful life or "Type A" behavior on the risk of developing coronary heart disease (CHD) has been recognized. 16, 17 Type A individuals tend to have an accelerated pace of life, competitive drive and severe sense of time urgency.¹⁷ The role of stress in contributing to or aggravating gastrointestinal disorders is commonly accepted, although hereditary factors undoubtedly play a part.

The evidence to indicate an increased need for nutrients during stress is not well-established. Most evidence of increased nutrient needs or a "protective" role of nutrients with stress are ancecdotal. There are, however, scattered reports of controlled observations regarding this issue.

Scrimshaw, et al., reported greater variation in the excretion of urine nitrogen in college students during exams than during the pre-exam period.² This increase was not considered to be of sufficient magnitude or duration to warrant an increase in the Recommended Dietary Allowances (RDA) for protein.¹²

The nutrient most often associated with emotional stress is vitamin C. Stress-responsive tissues, such as the pituitary and adrenal glands, contain the highest concentrations of this vitamin in the body and adrenal vitamin C is decreased in response to stress. ¹¹ Unfortunately, there has been only a single report of increased excretion of vitamin C in a subject participating in a metabolic study, when two fellow prisoners who were also metabolic study subjects escaped during the study. ¹⁸ This report, however, involved only one subject, was made as a secondary observation, and did not control other factors which may also have influenced the alteration in metabolism of the vitamin that was observed.

Compared to the inexact testimonials frequently given by the lay person, the existing scientific evidence does not support the claims of beneficial effects of consuming greater than the RDA level of nutrients to protect against stress. It is assumed that the RDA level for the nutrients includes an adequate margin of safety to accommodate possible transient changes in nutrient requirements that might occur with the stress of life.¹²

Eating habits may change. Some people eat less during periods of stress, while others tend to eat more. The result of this could either be overnutrition or undernutrition, obviously depending on the change in eating pattern. Consuming a well-balanced meal, even during periods of emotional stress, is crucial for health.

Summary: Physical stresses of illness and injury result in clear increases in caloric and protein needs and perhaps vitamin and mineral requirements that remain elevated until the repair process is complete. Extremes in temperature have less effect on nutrient needs. Greater nutrient needs with emotional stresses have not been clearly documented, although changes in eating behaviors have been noted. Malnutrition, either pre-existing or developing as a result of the stress, is in itself a stress to the body. Thus, malnutrition may interfere with the process of adaptation to stress and impair the recovery process.

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AMERICAN ACADEMY OF PEDIATRICS

LEARNING DISABLED CHILDREN HAVE TROUBLE IN EARLY ADULTHOOD

A learning disability is something that, unfortunately, never goes away. It is a chronic disorder that requires special attention throughout a child's school career.

What's more, coming from a highly educated, wealthy family can provide only limited help. In a new 10-year follow-up study of 114 learning-disabled students, it was found that few of them will continue onto college and the professions.

The report, conducted by Harry Hartzell, M.D., and Carolyn Compton, Ph.D., both from Stanford Medical School's Department of Pediatrics, notes that significantly lower levels of school attainment, academic and social success were found in the learning disabled-group when compared to 144 nondisabled siblings.

The doctors, writing in the December issue of Pediatrics, the journal of the American Academy of Pediatrics (AAP), nevertheless did reveal some important information that might aid these students. "If family means are available, private tutoring seems to be a particularly helpful intervention, in part due to its anonymity," Drs. Hartzell and Compton said.

Students interviewed said placement in a special day class, a measure of severe academic disability or social problems, hindered academic and social success.

Factors that contributed to a learning-disabled student faring better in school were: a positive personality, good home life, family wealth, family support, high IQ, participation in sports and work experience in high school.

Conversely, the study said, a severe learning disability, a disability in math and/or hiperactive behavior caused less success.

Drs. Hartzell and Compton concluded that these findings have important implications for those medical and educational personnel who counsel parents of young children with learning disabilities. They said parents needs to know that a learning disability is a disorder that can never be fully remediated.

"Because the effects of the disability are still seen in adulthood, it is important that students get a great deal of support and encouragement as they deal with academic pressures and related social problems. Encouraging students to develop interests in out-of-school activities and fostering their strengths in nonacademic skills will help them to achieve not only social success, but academic success," the doctors said.

Particularly helpful for learning-disabled students is a job in junior or senior high school, because of the positive feelings feelings of worth. In addition, the study results noted that vocational and career counseling were important to these adolescents.

However, the doctors warned that family expectations of the student's school success should be realistic and based on a knowledge of the student's IQ and degree of disability.

TESTICULAR CANCER: WHAT MEN DON'T KNOW CAN KILL THEM

—Unlike the success of women being taught about examining their breasts to detect cancer, men have seriously lagged behind in checking for testicular cancer—the third leading cause of cancer death for men aged 18-40.

Those findings, reported in the December issue of Pediatrics, the journal of the American Academy of Pediatrics (AAP), found that young adult men are unaware of their risk to this type of cancer. John Goldenring, M.D., and Elizabeth Purtell, RNNP, from Loyola Marymount University, Los Angeles, surveyed a group of male college athletes on their knowledge of early cancer detection techniques. They found that 87 percent of the males were almost completely unaware of their risk for testicular cancer.

Only 9.6 percent had been taught testicular self-examination, the study continued, and only half of these self-exams were a result of a physician teaching them the techniques. Six percent actually examined themselves regularly.

Conversely, 60 percent of the women athletes surveyed had been taught breast self-examination (75 percent by a physician), and about 33 percent of them were doing regular exams.

Though only one in 50,000 males contracts testicular cancer, it is quite easy to detect and is almost 100 percent curable when detected early.

The researchers said physicians are simply not informing young males about this risk, nor are they teaching them self-examination of the testes. They remarked that people of all ages, but particularly young people after puberty, should be encouraged to perform self-examinations on a monthly basis.

AMERICAN COLLEGE OF PHYSICIANS



OCCUPATIONAL HEALTH: ACP EXAMINES THE ROLE OF MEDICINE

Physicians have an obligation to their patients and the public to recognize, treat, and work to prevent occupa-

tionally related illness and injury, says the American College of Physicians (ACP).

The national medical specialty society, in a recent position paper urged its members and all physicians to take an active role in their patients' occupational health needs— a role as crucial as that of managing problems caused by other known health risks, such as smoking and obesity.

"Millions of workers in this country are exposed to silica, asbestos, cotton, and other dusts" suspected of causing occupational lung disease, says the College statement. Many other workers risk the effects of daily exposure to the more than 300 billion pounds of synthetic organic chemicals produced yearly in the United States, and more diseases are being linked to specific chemicals. According to the 1979 Surgeon General's Report on Health Promotion and Disease Prevention, "There is virtually no major chronic disease to which environmental factors do not contribute, directly or indirectly."

The growing awareness among workers of the dangers associated with some work environments leads many to consult with their physicians about the safety of their jobs, the ACP says. This, coupled with the growing amount of scientific and medical evidence about particular work-related dangers, has prompted the College to help its members and other physicians become more knowledgeable about occupational health and the risks to which their patients may be exposed.

In order to discover possible job-related risks and the source of job-related health problems, the ACP advises physicians to keep an occupational history along with the medical history of all patients of working age. Several examples of occupational history forms, developed by the Occupational Health Committee and by the Arizona Center for Occupational Safety and Health, are included with the statements; each enquires into the patient's work background and that of family members and questions the patient about past and present exposure to known hazards.

Because medical education has traditionally neglected training in occupational health, the ACP recommends that the medical community increase both the quantity and the quality of courses and training programs in occupational medicine. The College also urges physicians to increase their own knowlege of occupational and environmental risks, and has attached for further reference a bibliography (derived from one by the American Occupational Medicine Association) and "Sentinel Health Events (Occupational): A Basis for Physician Recognition and Public Health Surveillance," by D.D. Rutstein et al. (American Journal of Public Health 1983; 73(9): 1054-1052; reprinted by permission). The latter lists events that signal the need for intervention, the causative agent and related industries and occupations.

The ACP paper also addresses the confidentiality of medical records and the physician's obligation to a patient's employer when performing pre-employment screening examination, giving periodic health examinations and reporting for cases involving workers compensation. "The physician's obligation to the patient's employer... is limited to provision of medical advice only

about the patient's ability to work with or without restrictions," the ACP says. Also, according to the ACP, "the physician has an obligation to inform the patient of the findings and their implications. The patients should be informed if any disability or disease may be work-related and possibly compensable under law".

The College believes that physicians —both individually and collectively— have an added responsibility to improve the health of the public. The ACP suggests several ways in which physicians can fulfill this responsibility: by encouraging good health practices in the workplace, by practing medicine in industrial settings, by developing and implementing a national system of occupational health surveillance, and by influencing legislative and regulatory approaches to securing a safe, healthy environment.

American College of Emergency Physicians

WATER INTOXICATION

Your baby is ill, and in an effort to speed recovery you take the child off its formula and give the infant only water. Unfortunately, your good intentions may result in a sometimes fatal condition known as water intoxication.

According to an article in the January issue of *Annals of Emergency Medicine*, water intoxication involves excessive intake of water. In addition to the feeding mismanagement of infants, water intoxication may follow overzealous drinking, swimming lessons, or the use of diluted baby formula.

The article's author, Robert E. O'Connor, MD, Department of Emergency Medicine, Wilmington Medical Center, Wilmington, Del, cites the following symptoms of water intoxication: restlessness, weakness, nausea, vomiting, diarrhea, and convulsions.

In his article, Dr. O'Connor reports the case of a previously healthy two-month-old girl. Because of continued vomiting, the infant was given 20 to 30 ounces of water daily for three consecutive days, instead of her usual formula. She was admitted to a medical facility after convulsions began, and was diagnosed as having water intoxication.

Dr. O'Connor says the condition of water intoxication may be more common than previously thoughy, but it is preventable. Prevention consists of giving the infant clear liquids that contain a solute such as sugar water, flat soft drinks, or juices. Plain water should be used sparingly. Common treatment for the condition consists of fluid restriction and salt replacement.

What can you do for hypertensives like these?



Rely on one-tablet-a-day for these and virtually

Laura K is depressed... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN® (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits ... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Smoking has been implicated—especially in males. Cardioselective **TENORMIN** exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence.

Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³

At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.
Although beta

blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood same degree as propranolol.

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen.
Unlike propranolol, cardioselective TENORMIN can reduce the likelihoo of bronchospasm in susceptible

patients.⁵



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"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy. ¹⁰



*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

TENORMIN® (atendol)

See following page for brief summary of prescribing information.





Therapy for virtually every hypertensive patient in your practice.

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[1-methylethyl) amino] propoxy]. Alenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23 It is freely soluble in 1N HCl (300 mg/ml at 25 °C) and less soluble in chlorotorm (3 mg/ml at 25 °C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihyperfensive agents, particularly with a thiazide-type duretic.

sion. It may be used alone to concomitatingly with other artimypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiact failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics. TENORMIN should be administered cautiously Both digitalis and atenole islow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be tully digitalized and for be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abruptic resistation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overtaingina pectors, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initlated
at 50 mg and a beta,-stimulating agent (bronchodilator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood
levels.

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery in this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycema and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal fevels. Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

onitored closely

should be monitored closely PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce verigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clondine.

of clonidine."

Carcinogenesis, Mutagenesis, Impalrment ot Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg /kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vaculation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolof/kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo /tetal resorptions in rats at doses equal to or greater than 50 mg /kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg /kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
Schottland rich to the fature. potential risk to the tetus

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

atenolol Pediatric Use: Safety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg. by checklist:—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-19%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0-2%), light-headedness (3%-0-7%), tiredness (26%-13%), tatique (6%-5%), lethargy (3%-0-7%), drowsiness (2%-0-5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
MISCELLANEOUS: There have been reports of skin rashes and 'or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered it any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. tored following dessation of therap

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenoiol)

TENORMIN (atenolot)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension,

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart tailure, hypotension bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Amnophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose.

Hypoglycemia: intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet aday either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMINI may be used alone or concomitantly with other antihypertensive agents including thiazide-type duretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/rmin. 1 73 m² (normal range is 100-150 ml/rmin/1 73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Atenolol Creatinine Clearance (ml/min/1 73 m²) Elimination Half-lite Maximum Dosage

(hrs) 15-35 <15 16-27 50 mg daily 50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolor) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolor) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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STUART PHARMACEUTICALS Division of ICI Americas Inc.

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Resumenes de La Literatura 7 VI édica

AMIODARONE TREATMENT OF CRITICAL ARRHYTHMIAS IN CHILDREN AND YOUNG ADULTS. Garson A, Gillette P, Mc Vey P, et al. J Am Coll Cardiol 1984; 4:749

Los autores, de la Escuela de Medicina de la Universidad de Baylor y el Hospital de Niños de Texas estudiaron los efectos de la amiodarona en 39 pacientes pediátricos con disritmias refractarias al tratamiento convencional. Se incluían pacientes con "flutter" atrial, taquicardia supraventricular y taquicardia ventricular. Un 36% de ellos eran casos post operados de cardiopatías congénitas.

La supresión de la arritmia ocurrió en 15 de 16 pacientes con flutter atrial, 11 de 14 con taquicardia ventricular y en 5 de 9 con taquicardia supraventricular. Los efectos secundarios sintomáticos fueron: erupción cutánea (3), cefaleas (2), nauseas (1) y neuropatía periférica(1). Siete pacientes tuvieron microdepósitos corneales asintomáticos que desaparecieron al descontinuar el medicamento. No hubo efectos secundarios en pacientes menores de 10 años. Otros efectos del farmaco fueron: bradicardia, prolongación del intervalo QT, y aumento en T₄ y "reverse" T₃. En un seguimiento de seis meses a 3 años, 21 pacientes (54%) tenían su arritmia totalmente controlada con amiodarona.

De esta experiencia los autores derivan las siguientes conclusiones:

- que la amiodarona es extremadamente efectiva en el tratamiento de niños con flutter atrial, taquicardia ventricular y taquicardia supraventricular refractoria al tratamiento con los farmacos antiarrítmicos convencionales.
- que el medicamento no empeora el fallo cardíaco por lo que es excelente para aquellos pacientes con contractilidad miocárdica disminuída.
- en los pacientes con flutter atrial a pesar de su marcada eficacia (efectiva en un 94%) puede causar bradicardia significativa.
- que la incidencia de efectos secundarios de importancia es baja, que no afecta el crecimiento de los niños y que hay cambios en la función tiroidea mientras lo estén tomando.

Los autores terminan enfatizando que los efectos a largo plazo de la amiodarona no se conocen, por lo que su uso se recomienda solamente en niños con taquiarritmias críticas y refractarias al tratamiento médico.

Rafael Villavicencio, MD, FACC

CENTERS FOR DISEASE CONTROL. ADULT IMMUNIZATION. RECOMMENDATIONS OF THE IMMUNIZATION PRACTICES ADVISORY COMMITTEE (ACIP). Morbidity and Mortality Weekly Report 1984, 33: Supplement 1

Este folleto de 68 páginas tiene el potencial para convertirse en uno de los manuales clásicos de referencia rápida para los médicos. Es comparable a un "PDR" o un "Washington manual" para vacunas. Presenta información sobre qué vacunas son recomendadas para personas saludables de cierta edad, ocupación, determinado modo de vida o plan de viaje. Uno de los capítulos indica las inmunizaciones recomendadas para personas embarazadas, inmunocomprometidas, en hemodiálisis, asplénicas, hemofilicas, alcohólicas o con otras dolencias crónicas, como diabetes. La segunda parte del folleto describe las indicaciones, efectos secundarios, reacciones adversas, precauciones y contraindicaciones de cada una de las vacunas e inmunoglobulinas en uso actualmente (aún las de uso exclusivo de las fuerzas armadas).

Casi la mitad del texto está dedicado a tablas sinópticas que resumen claramente la información presentada en los capítulos del folleto.

Nota: Se puede ordenar este impreso (utilizando el título arriba indicado) del "Superintendent of Documents, U.S. Government Printing Office", Washington DC 20402 y sólo cuesta un dólar.

José G. Rigau Pérez, MD, FAAP

EXAMEN ULTRASONOGRAFICO EN NIÑAS CON PUBERTAD PRECOZ: Shawker TH. J Ultrasound Med 1984; 3(7)

Cincuenta y seis niñas con signos de pubertad precoz fueron examinadas mediante la sonografía pélvica. Ovarios de tamaño adulto y un utero de tamaño intermedio fueron características de verdadera pubertad precoz ya siendo del tipo ideopático o debida a lesión del sistema nervioso central. En casos de telarquia prematura los órganos pélvicos eran de tamaño normal infantil mientras que en casos de seudo-pubertad precoz la apariencia de los ovarios y el utero variaba dependiendo del proceso causante. Quistes grandes de ovarios agrandados fueron encontrados en 6 pacientes con el síndrome de Mc Cune-Albright.

El estudio de sonografía diagnóstica de la pelvis es de benefício en la evaluación de niñas con desarrollo sexual precoz porque puede demostrar los ovarios de tamaño adulto de la verdadera pubertad precoz distinguiendo a esta condición de la telarquia prematura e igualmente puede demostrar causas específicas de pubertad precoz tales como tumores de ovarios y quistes de ovario.

Bernardo Marqués, MD

THE USEFULNESS OF BRONCHO-ALVEOLAR LAVAGE IN THE DIAGNOSIS OF PULMONARY INFILTRATES IN THE IMMUNOSUPPRESSED PATIENT. Stover DE, Zaman MB, Hadjo SI.

Ann Inten Med 1984; 101:1-7

This is a 2 years study of 92 immunosupressed patients with pulmonary infiltrates from the Memorial Sloan-Kettering Center in New York. These patients were selected prospectively and all of the them had pulmonary infiltrates. As their underlying condition they had received a bone marrow transplant, were receiving chemotherapy or other immunosuppresive drugs.

The diagnostic yield and complications of several diagnostic modalities were compared in the critically ill and thrombocytopenic (35 patients with less than 70,000 platelets mm³). The diagnostic modalities included open-lung biopsy, cutting-needle biopsy, needle aspiration, transtracheal aspiration, fiberoptic bronchoscopy (FOB) with transbronchial biopsy, brochial brushings and washings, and the bronchoalveolar lavage technique using 210 ml. of normal saline in the middle lobe or lingula in 30 ml. aliquots. Eighteen of these patients were in respiratory failure needing mechanical ventilation.

The study found that the bronchoalveolar (BAL) technique have a yield of 66%, been more effective for Pneumocystis carinii (18 of 22), cytomegalovirus (10 of 12), fungal pneumonia (5 of 6) and mycobacterial infections (4 of 5).

The technique was also helpful for the diagnosis of pulmonary hemorrhage (7 of 9). The technique was not as effective in the diagnosis of malignancy (10 of 22) or in the diagnosis of drug induced lung infiltrates (6 of 15).

The technique of broncho-alveolar lavage was found to be an accurate and safe method to sample alveolar cell content and secretions in both normal persons and patients with interstitial lung diseases including patients with thrombocytopenia, having the highest yield for opportunistic infections, and the lowest for pulmoary malignancy and drug toxicity. If the other diagnostic techniques are not feasible, broncho-alveolar lavage alone can be used as the initial invasive procedure for evaluation of diffuse pulmonary disease in the immunosuppressed patient.

Comment: This paper presents data on an effective alternative method to solve the diagnostic problem on the thrombocytopenic immunosuppressed patient with a lung infiltrate, giving the physician an additional tool to handle this difficult problem. Bronchoalveolar lavage seems safe and has a high diagnostic yield in pulmonary infections.

José L. Collado Marcial, MD

PATRONES CAMBIANTES DE LA GLOMERULONEFRITIS EN ENDOCARDITIS. Neugarten J and Baldwin DS. Am J Med 1984; 77:297

Los autores resumieron los hallazgos clínicos morfológicos de la glomerulonefritis que ocurre en el presente, en los casos de endocarditis bacteriana. Con la introducción de los antibióticos, con la desaparición de fiebre reumática y el aumento en el uso de drogas parenterales, la naturaleza de glomerulonefritis ha sido alterada. El staphylococcus aureus se ha convertido en una causa importante de endocarditis con una alta incidencia de glomerulonefritis. En un estudio postmortem, durante la era de antibióticos, la glomerulonefritis focal se encontró en 8% de los casos y la glomerulonefritis difusa en el 14%. S. aureus fue el agente etiológico más frecuente en endocarditis fatal y fue responsable por más de 50% de los casos de glomerulonefritis. El abuso de drogas fue la causa predisponente para el mayor desarrollo de endocarditis. Las correlaciones serológicas de endocarditis incluyen enfermedad de complejo inmune, ocurriendo hasta en un 90% o más de los pacientes, crioglobulinas mixtas en un 84-95% de los pacientes, factor reumatoideo en el suero en un 10-70% de los pacientes, e hipocomplementemia particularmente en aquellos pacientes con glomerulonefritis. Se ha postulado que la cascada alterna de complemento puede activarse secundariamente por los antígenos de la pared celular bacteriana. El complemento es probablemente el mejor factor a correlacionar con glomerulonefritis y con el grado de insuficiencia renal. Las manifestaciones clínicas de glomerulonefritis son muchas veces leves, con hematuria microscópica y con proteinuria en la mayor parte de los casos. Proteinuria significativa e hipertensión son raras. El deterioro renal con creatinina elevada es frecuente y puede ser una manifestación primaria de endocarditis en algunos casos. No hay correlación entre la duración de los síntomas antes de la presentación y los valores de creatinina iniciales o en pico. Con los antibióticos, el pronóstico de glomerulonefritis es generalmente bueno, con resolución de las anormalidades urinarias en varios días a semanas. A pesar de que muchos pacientes con uremia tienen un resultado fatal, el fallo renal severo ocasionalmente resuelve con terapia efectiva. Rara vez el fallo renal crónico puede ocurrir como una consecuencia de endocarditis a pesar de que se haya curado bacteriológicamente.

Comentarios: La endocarditis representa muchos tipos de una enfermedad que depende de los organismos que la causan v que envuelven una válvula o varias válvulas cardíacas. Los autores presentan los cambios en los patrones que se ven en glomerulonefritis en los pacientes con endocarditis como un reflejo de un aumento en incidencia de endocarditis por estafilococos. El riñón es uno de los lugares que se afectan más frecuentemente por endocarditis. La enfermedad renal puede presentarse como embolias focales de vegetaciones cardíacas, pielonefritis bacterianas o a un absceso renal. Ocasionalmente se ve bacteruria en pacientes con glomerulonefritis v esto refleja una enfermedad immune. Los estafilococos desarrollan una respuesta inmune en el huésped de tal manera de que el cuerpo desarrolla reacciones autoinmune en varios órganos, que son afectados, el riñón se convierte entonces en uno de los lugares que se afecta con más frecuencia. El diagnóstico de endocarditis-glomerulonefritis viene con proteinuria y hematuria. Fallo renal según descrito es mucho menos frecuente a pesar de que la severidad de la afectación renal en ocasiones puede requerir diálisis. Medidas de inmunidad ayudan en definir y seguir esta enfermedad. Niveles de complemento bajo o los niveles circulantes de complejos inmune en presencia de fallo renal y/o proteinuria y hematuria sugieren endocarditis asociada a glomerulonefritis. Según la endocarditis subvacente es tratada, estos síntomas usualmente se aclaran totalmente. Las recaídas o resistencia a tratamiento puede muchas veces medirse en términos de los parámetros de inmunidad asociados con este tipo de glomerulonefritis. La glomerulonefritis puede ser causada por otros factores además de endocarditis bacteriana. Los antibióticos pueden inducir una nefritis intersticial o una glomerulonefritis inmune. La glomerulonefritis intersticial puede definirse por la presencia de eosinofilia y eosinofiluria. En ambos tipos de lesión renal se caracteriza por una mejora en la condición renal una vez se disminuye o se descontinúa el antibiótico específico. Es importante aclarar que la glomerulonefritis puede ser inducida por medicamentos y no responder a antibióticos. El clínico debe estar consciente que esta forma de enfermedad renal, sin tomar en cuenta su inicio etiológico, puede ser lo suficientemente grave como para requerir diálisis a corto tiempo y es posible que a largo tiempo. En algunas circunstancias, el uso de corticoesteroides puede considerarse y ser de beneficio al tratamiento.

Carlos Ramírez, MD, FACP

COMPARISON OF DIETARY PROTEIN WITH AN ORAL, BRANCHED CHAIN-ENRICHED AMINO-ACID SUPPLEMENT CHRONIC PORTAL SYSTEMIC ENCEPHALOPATHY: A RANDOMIZED CONTROLLED TRAIL. Horst D, Grace MD, Conn H.O. et al Hepatology 1984; 4:279-287

Los pacientes con cirrosis hepática crónica con frecuencia no toleran mucha proteína en la dieta porque desarrollan encefalopatía. Esta limitación en la ingesta de proteína puede resultar en un balance negativo de nitrógeno que es nocivo nutricionalmente, podría resultar en una dis-

minución de la masa muscular corporal y contribuir a un deterioro en la función hepática. Hay evidencia en estos pacientes de alteraciones en las concentraciones séricas de aminoácidos. Se encuentran las concentraciones de aminoácidos aromáticos elevados y los ramificados disminuidos. En este estudio se randomizaron 37 pacientes con cirrosis crónica e intolerancia a más de 40 gramos de proteina en la dieta a recibir un suplemento dietético nuevo que continue altas concentraciones de los aminoácidos ramificados y baja cantidad de los aromáticos o a un incremento de proteina en la dieta. Se estudiaron los pacientes hasta que recibían un total de 80 gramos de proteina en la dieta o el desarrollo de grado 2 de encefalopatía. Todos los pacientes recibieron una dieta con 20 gramos de proteina por una semana y después recibían permanentemente un incremento de 20 gramos de proteína en la dieta o en el suplemento de aminoácidos. Se encontró que los pacientes que recibieron el suplemento diétetico de aminoácido toleraron una cantidad mayor de nitrógeno sin desarrollar encefalopatía. Estos resultados pueden ser de utilidad clínica en los pacientes con limitaciones de proteina en la dieta.

Angel Olazabal, MD, FACP

CONDUCTION BLOCK AND DENERVATION IN GUILLAIN-BARRE POLYNEUROPATHY. Brown WF, Feasby TE. Brain 1984; 107:219-239

Over 20 patients with acute Guillain-Barré syndrome were evaluated for electrophysiological abnormalities of peripheral nerves. Most were initially seen by two weeks after onset. The two main abnormalities were: conduction block in a peripheral nerve and low maximum M amplitude. Maximum motor and sensory conduction velocities were often normal and temporal dispersion was relatively less common. Conduction block was not well localized in some peripheral nerves; while in others, there was a focal block near the proximal or distal portion of the nerve. Conduction abnormalities were frequent at the common sites of entrapment. A low compound motor action potential early in the course of the disease appeared to correlate well with the subsequent development and frequency of denervation in the muscles examined, as well as with an unfavorable clinical recovery. Conclusions from this study are that conduction block is the main cause of acute symptoms in Guillain-Barré syndrome and that subsequent axonal degeneration contributes to the variability of the acute disorder and is the main cause of lasting disability.

Herman J. Flax, MD

VALUES OF EARLY ATTENTION TO SPINAL COMPRESSION SYNDROME:
Hejgaard N, Larson E; Acta Orthopedica Scandinava
1984; 55:234-237

Compression of the spinal cord and cauda equina always involves a serious risk of disabling sequelae. The prognosis depends not only on the etiology, but also on

the failure to make the correct diagnosis and the therapeutic delay. Diagnostic delay may be caused by the widely different etiologies with varying symptoms and signs causing the syndrome. In this article the authors discuss a study of 125 patients with this diagnosis, their initial symptoms, and the time interval between the appearance of symptoms and the treatment. Seventy-two patients suffered from malignant diseases. Among the malignant etiologies, the one most commonly found was metastasis, mainly from Hodgkin's disease, and myelomatosis, followed by lymphoreticulosis. Most patients with benign diseases had intraspinal affections of soft tissues mainly herniated nucleus pulposus, neurinoma, and meningioma. Only patients with spondylosis had bone involvement. Early symptoms most frequently found in malignant diseases were pain (70-80%), sensory loss (50-60%), paresis (30-34%) and last, sphincter dysfunction. In patients with benign diseases (HNP) the first symptom was usually paresis, followed by pain and sensory loss with bone involvement. In patients with spondylosis and an average of six weeks of progressive symptoms and signs had elapsed before they consulted a physician and therefore, had a clear reason for a therapeutic delay. Among other etiologies there was no clear cause to explain treatment delay. The authors concluded that a deficient diagnostic recognition is the only explanation for this therapeutic delay.

Anna V. Cintrón, MD

MALLET TOES, HAMMER TOES, CLAW TOES AND CORN. Coughlin M. Postgraduate Medical 1984; 75:191-198

The term Mallet toes, Hammer toes and Claw toes has been used interchangeably; their definition is somewhat confusing. Basically, a mallet toe involves a contracture of the distal IP joint in which the distal phalanx is fixed on the middle phalanx. A hammer toe involves a similar contracture of the proximal IP joint in which the middle and distal phalanges are plantar flexed in relation to the proximal phalanx. A claw toe has a dorsiflexion deformity at the MP joint associated with a hammer-toes deformity. All three of these deformities may be passively correctable in the early stages or rigidly fixed in a more chronic situation. Mallet toe is usually secondary to highheeled-pointed-toe shoes; also hammer toe can be secondary to shoe problems; rheumatoid arthritis and psoriatric arthritis. Claw toe may be secondary to arthritic degeneration, diabetes mellitus and neuromuscular diseases.

The term "corn" describes the buildup of callus over a bony prominence in one of the lesser toes. The term "hard corn" to a formation over the lateral aspect of the fifth toe. The term "soft corn" refers to the development of a pressure point in the web space between two of the lesser toes. Conservative treatment centers around shaving keratotic lesions as well as relieving pressure from the overlying bony prominence. When a corn is refractory to conservative care, physical intervention may be contemplated.

José R. Busquets, MD

SINCOPE INDUCIDO POR NEURALGIA DEL GLOSOFARINGEO: LA INERVACION DEL SIMPATICO A LOS MUSCULOS. Gunnar WB, Werlerberg, CE, Surdlof, G Neurology 1984; 34:552-4

Se estudió a un paciente el cual desarrollaba regularmente períodos de asístole y episodios de desmayos durante los ataques de neuralgia del glosofaríngeo. El marcapasos cardíaco no previno el síncope. La actividad espontánea del simpático en los nervios que van a los músculos desaparecieron durante los ataques y la presión sanguínea bajó a pesar del funcionamiento del marcapasos.

El desmayo probablemente resultó de la conducción anormal de los impulsos aferentes de la zona de "trigger neuralgia" en la faringe a el tallo del cerebro en los centros vasomotores.

Probablemente el marcapasos falló en prevenir el síncope debido a la inhibición profunda del simpático, la cual coincidió con la excitación vagal cardíaca.

Carmen N. Lebrón, MD

TREATMENT OF STUMP WOUND HEALING PROBLEMS IN THE VASCULAR AMPUTEE. Stern P. Orthopaedic Review 1984; (13) 8:450-455

El retraso en la cicatrización de un muñon después de una amputación de la extremidad inferior secundario a enfermedad periferovascular es la causa principal de diferir el uso de próstesis y prolongar la estadía hospitalaria.

Este artículo presenta un estudio realizado en el Centro de Rehabilitación de Burke. Diecisiete (17) pacientes que tenían problemas en el muñón (dehiscencia, cambios de piel isquémicos e injertos de vena infectados) fueron tratados con Debrisan. El Debrisan, explica, tiene un efecto físico para secar las heridas exudativas y absorbe las infecciones locales de bacterias por acción capilar. De los 17 pacientes, ninguno necesitó conversión de la amputación, y sólo una necesitó revisión. El Debrisan demostró ser efectivo en el tratamiento de estos pacientes.

Mabel Cabán, MD



NICOTINE GUM HELPS SOME BREAK ADDICTION

Nicotine chewing gum is twice as effective as placebo in helping smokers who wish to quit, according to a report in JAMA.

In the first study of its kind, which was conducted at Sahlgren's Hospital in Goteborg, Sweden, 250 smokers who wanted to quit participated in a controlled, double-blind, randomized trial. One hundred six used a chewing gum with 2 mg of nicotine and the other 99 used a placebo gum with a nicotine flavor. Both groups also received group therapy and information about the benefits of quitting smoking.

Agneta I. M. Hjalmarson, PhD, reports that 29 percent of those who used the nicotine gum remained abstinet after one year compared with 16 percent of those treated with placebo. More subjects in the nicotine group said that the gum reduced their desire to smoke, and they tended to use the gum longer. Three percent were still using the gum after two years, while none in the placebo group were still using the gum.

In a related article, John R. Hughes, MD, of the University of Minnesota, Minneapolis, and Stephen A. Miller, MS, of Merrell Dow Pharmaceuticals, Inc., Cincinnati, say that successful use of the gum depends on appropriate instructions, expectancies and adjunct therapies. The gum has been approved as a prescription drug and is contraindicated only for those with severe cardiovascular disease and pregnant women.

There are some other conditions (hypertension, ulcers, diabetes, hyperthyroidism, esophagitis) that may be aggravated by nicotine in the gum, but the researchers point out that smoking results in higher blood levels of nicotine and is generally more harmful.

In the "Question and Answers" section of JAMA, Manuel L. Karell, MD, asks whether use of nicotine gum will result in "gum addicts." McKendree E. McNabb, MD, replies that only about seven to 10 percent of those who use the gum are reluctant to give it up after three to six months. Studies show that plasma nicotine levels after chewing the gum are less than half the levels found after smoking tobacco. McKendree also notes that smokers are exposed to carcinogens, carbon monoxide, and cyanide from cigarrettes.

JAMA Nov. 23, 1984

OLDER MOTHERS HAVE HIGHER RISK FOR STILLBIRTHS

Women who become pregnant during their late thirties have twice the risk for late fetal death as women in their early twenties, according to a study reported in the *Journal of the American Medical Association*. The study also showed that women aged 35 to 39 have significantly greater risks of delivering preterm or low birth weight infants.

Michele R. Forman, PhD, of the Centers for Disease Control in Atlanta, and colleagues base their findings on data from nearly 175,000 births in Sweden between the years 1976 through 1980. They studied three groups of women ranging in age from younger than 20 through 39 years. The first group included women pregnant for the first time; the second group, those who had had a previous pregnancy that ended in abortion or miscarriage; and the third group included those who had had one successful pregnancy.

The researchers found that compared with women aged 20 to 24, all women older than 30 had higher risk for stillbirth but the relative risk was significantly greater for women aged 35 to 39 years: In the first group, those women had a relative risk of 1.76; in the second group, 2.22; and in the third, 2.39. Mothers in their 30s in the first two groups also had a higher risk for bearing premature or low birth weight infants (significantly higher in the first group) compared with women aged 20 to 24. These risks increased with maternal age after 30.

Risks were somewhat lower for women aged 30 to 34 who had had one successful pregnancy (the third group). The risk for stillbirth in this category was significantly lower than for women of the same ages in the first two groups. Also, women in the third group aged 30 to 34 had approximately the same risk for preterm or low birth weight infants as women aged 20 to 24. The only risk that decreased with maternal age was early newborn death, also for women who had had a previous successful pregnancy, the study showed.

The Swedish data has important implications for prenatal care in the United States, where many women are postponing pregnancy because of careers, the researchers conclude. Their study showed that overall, women who become pregnant during their 30s are more likely to experience adverse outcomes than women in their early 20s, and that most risks increase with maternal age. "These findings are important to the current increase in first births among white women aged 30 through 34 years and to projections of a further increase in births to women aged 30 through 39 years," they say.

JAMA Dec. 14, 1984

NEW KIDNEY STONE TREATMENTS INVESTIGATIONAL: AMA

The new shock-wave treatment for kidney stones remains an investigational procedure, according to the American Medical Association Diagnostic and Therapeutic Technology Assessment (DATTA) program.

Reporting in JAMA, the DATTA panel of physicians called both noninvasive extracorporeal lithotriptoscopy (the shock-wave treatment) and endoscopic transurethral nephrolithotomy investigational. The panel said that percutaneous nephrolithotomy, a third approach to kidney stone treatment, is an established medical procedure. Opinion was closely divided on the first two procedures.

Developed in Germany, extracorporeal lithotriptoscopy uses shock waves to destroy kidney stones. During treatment, patients are immersed in a water bath containing a shock-wave generator. Waves will travel relatively unimpeded through tissue with densities close to that of water but will tear and shear mediums of substantially different densities, such as stones.

"Complete disruption of a kidney stone may take 1,500 separate shock waves," according to the DATTA report in the Questions and Answers section of the *Journal*. Stone fragments pass down the ureter. The therapy lasts 30 to 40 minutes and hospitalization lasts four days. Of the DATTA panelists, 14 said the procedure was safe and effective; 15 said it was investigational.

Opinion was identically divided on endoscopic transurethral nephrolithotomy, which uses both a flexible instrument to locate stones in the bladder, ureter and renal pelvis, and lithotripsy to destroy them.

"They appear to be effective methods of stone disruption when a ureteropyeloscope can be used," the report says. "Insufficient published data are available to comment conclusively on the safety of the procedures and assessment of their relative merit."

A solid majority of the panelists, 21 of 26, found percutaneous nephrolithotomy an established medical procedure. The procedure involves placement of a nephrostomy tube to allow passage of various urologic instruments. "There have been no randomized controlled trials, but the published literature and the experience of the DATTA panelists support the safety and efficacy of the procedure," the report says.

JAMA Dec. 21 1984

CESAREAN SECTIONS: STILL TOO MANY?

The number of cesarean sections performed in the United States has continued to increase despite evidence that many are unnecessary, according to a report in JAMA.

Norbert Gleicher, MD, of Mt. Sinai Hospital Medical Center and Rush Medical College, Chicago, concludes that a 1980 consensus conference sponsored by the National Institute of Child Health and Human Development was ineffective in curbing the trend toward more cesarean sections. The conference called for improved methods of fetal monitoring and consideration of vaginal delivery for women who had had a previous cesarean section and for women with breech presentations.

But in an editorial, Mortimer G. Rosen, MD, of Cleveland Metropolitan General Hospital, challenges Gleicher's conclusion. Rosen says more time is needed to assess the trends in the rate of cesarean sections. He points out that Gleicher studied only the years 1977 through 1982 and specifically noted the continued increase during the two years after the September 1980 conference. Rosen says reports from the conference were not published until 1981, and he suggests this is too short a time to change hospital, patient and physician attitudes.

Both physicians agree that better evaluation of cesarean sections are called for because of their increased risks and higher costs compared with vaginal deliveries. Gleigher reports that a cesarean section requires a mean extra maternal stay of 3.1 days, and since the infant also stays in the hospital, this results in twice the cost. "At a mean daily hospital rate of \$250, the additional charge per unecessary cesarean section would be at least \$1,550." He adds, "The general applicable mortality rate for cesarean delivery seems still to be two to four times higher than that for vaginal delivery."

Gleicher also notes that financial incentives now favor cesarean sections, which may require less of the physician's time and command higher rates than vaginal deliveries. Another disturbing fact is that cesarean section rates are not necessarily associated with high risk populations. Teaching hospitals have lower cesarean rates than either urban hospitals of different sizes or rural hospitals. Perinatal centers (level III institutions) have significantly lower cesarean section rates than level I hospitals.

"While hospital accreditations, perinatal designations and residency program approvals do require the maintenance of perinatal statistics, including cesarean section statistics, the rates themselves are seldom critically reviewed." Gleicher adds, "A significant decrease in the nation's cesarean birth rate can only be achieved if more rigorous cesarean section rate data are required from physicians and obstetrical departments."

Rosen says there are indications that changes are occurring. At 1984 meetings with more than 1,000 obstetricians in attendance, 90 percent said they would offer the option of vaginal delivery for patients who had had a previous cesarean section. Rosen notes that before the 1980 conference, more than 90 percent of obstetricians would not have done so. He concludes, "I think the authors should return to this issue in about five years when we may be able to document a plateau or even a decline in the cesarean birth rate."

JAMA Dec. 21, 1984

CORTICOSTEROIDS EFFECTIVE IN TREATING TOXIC SHOCK

Corticosteroids administered within two to three days of onset of toxic shock syndrome are effective in reducing the severity of illness and the duration of fever, according to a report in JAMA.

James K. Todd, MD, of the University of Colorado School of Medicine, who discovered and named the syndrome, and colleagues reviewed hospital records of 45 patients who had toxic shock syndrome. Twenty-five of these patients had received corticosteriod therapy during

the acute phase of illness. They found that compared with the 20 controls who had similar symptoms and otherwise similar treatment, those who received corticosteroids had "notable significant differences of a shorter duration of fever and a more rapid return to a stable clinical condition."

"The groups were comparable for age, sex, weight, year of admission, day of illness hospitalized, minimum systolic and diastolic blood pressure, severity of illness, co-intervention with antimicrobials and antipyretics, and amount of intravenous fluid received." The researchers note that the corticosteroid most commonly used was methylprednisolone sodium succinate, and therapy lasted approximately three days. They add that despite its short-term effectiveness, corticosteroid therapy has a potential detrimental effect on the immune response, which should be studied further.

In an editorial, Bruce B. Dan, MD, a senior editor with JAMA, says, "while measures for reducing the risk of acquiring toxic shock sydrome have been detailed, optimal treatment for the disease, once begun, is difficult to state." Dan adds that although corticosteroids have been shown to be effective, prospective trials are needed. He stresses that the most important preventive measure is to continue to educate young women about the risks of staphylococcus aureus infection associated with the use of tampons.

In a related article, Steven D. Helgerson, MD, MPH, of the Centers for Disease Control, and colleagues report on the risk of recurrence of toxic shock syndrome. They collected follow-up data on 53 cases in Oregon between 1980 and 1982. The researchers attribute the low recurrence rate (only one probable case) to two factors: 91 percent of the patients were initially treated with beta-lactamase-resistant antibiotics and only 44 percent of women resumed the use of tampons after the initial episode.

JAMA Dec. 28, 1984

BREAK DANCING CAN CAUSE INJURIES TO NECK, BACK, SCROTUM

Break dancing injuries to the testes, neck, back and head are described in the Letters section JAMA.

Ronald E. Wheeler, MD, and Rodney A. Appell, MD, of Louisiana State University Medical Center tell of two cases of testicular torsion in break dancers. They boys, aged 12 and 16 years, came to the emergency room because of acute scrotal pain that occurred after break dancing. Both were later found to have testicular torsion. The authors conclude, "While this does not necessarily imply that break dancing causes testicular torsion, the presence of acute testicular pain following this latest fad can lead physicians to conclude a traumatic cause for the pain when, in reality, an underlying true testicular torsion may be present requiring surgical intervention."

Partial dislocation of the neck is described in another letter from Bertha Ramírez, MD, and colleagues from New York Medical College. They report on a 15-year-old break dancer seen in the emergency room after

experiencing a "snap" in his neck followed by persistent stiffness. The patient said he had spun on his head the night before as part of a break dance routine. Examination revealed marked tenderness over the third through the seventh cervical vertebrae, with some muscular spasm and loss of sensation in his right arm.

Philip J. Goscienski, MD, and Louis Luevanos, MD, of the University of California, San Diego, report the case of an 11-year-old boy who experienced painful swelling of the midback because of back spins performed while break dancing.

The authors also report two other cases of this same injury, as well as two fractures of the radius, two fractures of the clavicle, a cervical dislocation, torn ligament of the knee, neck strain and severe sprains of the ankle and the thumb. "Before the 'breaking' fad passes, the medical profession will witness these and other injuries," the researchers say, "Most of these problems are minor, but the potential for severe and life-threatening injury is great."

Another letter, from Stuart M. Copperman, MD, in Merrick, NY, describes patchy baldness (alopecia) in two 17-year-old boys who had been practicing break dancing. "The constant spinning on the top of the head had eroded the hair shafts down to the scalp," he reports.

JAMA Dec. 28, 1984

DRUG TREATMENT FOR CHRONIC TONSILLITIS

Chronic tonsillitis in young adults may be treatable by drugs instead of the more often used surgery, according to a new report in the December 1984 Archives of Otolaryngology. Chronically inflammed tonsils in adults contain more scar tissue, possibly impairing penetration of antimicrobial agents, say Itzhak Brook, MD, MSc, of the Uniformed Services University for the Health Sciences, Bethesda, and Paula Yocum, of George Washington School of Medicine. Earlier use of clindamycin hydrochloride and lincomycin hydrochloride might prevent chronic infection, they add. The superiority of the drugs may be due to effectiveness against a wider range of microorganisms.

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NUESTRA PORTADA

Trópico. Oleo sobre lino del artista puertorriqueño Jorge Rechany. El autor nació en el Viejo San Juan en 1914 y a los 16 años comienza sus estudios de pintura con el profesor Alejandro Sánchez-Felipe. Luego de dos años estudia con el pintor Ramón Frade y en 1936 va a la National Academy of Design en Nueva York donde permanece hasta 1940. En la década del 50 viaja a México donde realiza estudios en la Escuela de Escultura y Pintura y en el Instituto Nacional de Bellas Artes. A principios de los años 60 se traslada a Europa y en viaje de estudios llega a Italia luego Holanda, Inglaterra, Francia y España. Luego de unos años en Puerto Rico el artista regresa a Nueva York en 1974 para continuar estudios en el Pratt Graphic Center de esa ciudad.

El artista ha expuesto sus obras en las principales galerías de arte de Puerto Rico, América y Europa, le han sido concedidos numerosos premios y distinciones tanto nacionales como internacionales y sus obras se encuentran diseminadas en colecciones públicas y privadas del hemisferio americano y europeo. Entre estas últimas cabe seña lar que es Rechany el único artista puertorriqueño con una obra en el Vaticano. Es un óleo-La Magdalena-que se encuentra expuesto en el Museo Vaticano de Arte Sacro Moderno en la Ciudad del Vaticano, Roma.

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico quiere agradecer la gentileza del autor de permitir su obra en nuestra portada así como al Dr. Edgardo García-Trías cuyo interés hizo que esto fuese posible.

EDITIORAL

On Chemotherapy, Pain and Cancer

"No patient should ever wish for death because of his physician's reluctance to use adequate amounts of effective narcotics".

L. S. Goodman and A. Gilman (1975)

In this issue of the Boletín de la Asociación Médica de Puerto Rico Dr. José Ramírez Rivera presents an important work that deals with a group of subjects very close to physicians involved in the care of cancer patients. He comments in a candid, yet direct fashion on the ethics of prolonging life with cytotoxic agents, and on the frequent inadequacies in the management of pain in persons with advanced malignancies. As a Hematologist-Oncologist I basically agree with the authors viewpoints.

On Chemotherapy and Cancer

The use of cytotoxic drugs in the treatment of cancer is here to stay. When cured cancer is defined as five years or more of a patient been alive, without evidence of recurrence and without further anticancer treatment, then chemotherapy can cure a significant number of patients:

- a) 50% of cases of children with acute lymphoblastic leukemia¹
- b) 68% of patients with Hodgkins disease stage III or IV^2
- c) 40% of patients with advanced stages of diffuse histiocytic lymphoma³
- d) Up to 90% of patients with non-seminomatous cancer of the testicles⁴
- e) 90% of patients with choriocarcinoma.⁵ In other tumors, although a cure cannot be attained, the disease can be controlled totally or subtotally in 50 to 80% of patients for an extended period of time for an average of 1 to 2 years. Among these malignancies are included; adenocarcinoma of the breast, epithelial carcinoma of the ovary, malignant lymphomas, multiple myeloma and acute myelogenous leukemia.

Therefore, in a large number of cancer patients, cure or effective long-term palliation can be achieved with the use of cytotoxic drugs. But the real problem is that too large a number of malignant tumors are resistant (fully or partially) to the currently available anticancer medications. If we add that the side effects of these agents are

formidable, often devastating to the patient - the panorama of cancer chemotherapy is far from rosy.

Thus a careful distinction must be made by the clinician between conventional chemotherapy, investigational chemotherapy and use less chemotherapy. Conventional chemotherapy is the use of tried and true drug combinations, that can predictably bring complete or partial control of a patient's cancer for a long period of time, often measured in years. Research chemotherapy is a necessary evil. In this setting the patient knows he or she will die of cancer, and agrees voluntarily to be used as a subject in which new drugs will be assayed. This is an invaluable and indispensable tool in the advancement of cancer treatment.

A further type of cancer chemotherapy -if such can it be called- is that in which advanced cancer patients are given drug combinations which are marginally effective, in an attempt to add a few more weeks of life to the patient. I believe this is the form of chemotherapy alluded to by Dr. Ramírez-Rivera in his paper. It is distressful to see patients with advanced tumors such as esophageal carcinoma, epidermoid carcinoma of lung, disseminated malignant melanoma, carcinoma of pancreas, and bladder carcinoma receiving aggresive chemotherapy out of an investigational setting. Why do some physicians give therapy that in all probability will not benefit the patient, is beyond me. I theorize that they are hoping for a miracle to happen. In this last group of patients I deeply agree with Dr. Ramírez-Rivera. If you are not going to help a patient, then cause him no further disconfort.

On Pain and Cancer

The management of pain in the cancer patient is a basic skill of the clinical practice of Oncology. Ignorance or disregard of this aspect makes the physician unworthy of caring for cancer patients. Nevertheless the subject of pain-releiving in individuals with advanced malignancies is not as simple as memorizing the doses of a number of drugs. A multidisciplinary approach is often required. Instances of this are: a) The use of a limited field of radiotherapy applied to a very painful metastasis.b) The installation of an epidural catheter for continuous infusion of narcotic analgesics. c) The judicious use of cordotomy and other neurosurgical ablative modes.

d) The use of intrathecal alcohol blocks and the use of peripheral nerve blocks. e) The concomitant use of psychotropic drugs such as phenothiazines, tricyclic antidepressants, and benzodiazepines, and even formal psychiatric treatment in patients whose cancer pain is magnified by mental illness.

Still, the narcotic analgesics are the backbone of cancer pain treatment. Five principles in the use of these substances that are too frequently missed by medical and paramedical personnel, according to Perry, are: a) Individuals vary enormously in narcotic dosage requirement. The concept of a "standard" dose is an error, so antipain medicine must be adjusted to individual response. b) The fear of overdosage with subsequent respiratory depression is exaggerated; tolerance to this adverse effect developes concomitantly with tolerance to the analgesic effect. Even if this rare complication should occur, it can rapidly be reversed with naloxone. c) Because narcotics are more effective in intercepting pain than in releiving pain once it becomes severe, an unnecessary delay between doses, (waiting for pain to become really severe to use the next dose), is ill-advised. d) Because of "first pass" liver metabolism, some narcotics require much higher oral dosage to obtain an effect equipotential to the parenteral route. e) The risk of iatrogenic "addiction" in dying cancer patients is negligible, and a distinction between physical dependence and drug abuse is easily determined.

Therefore the necessity of making pain management a building block in the formation and continued education of physicians dealing with cancer patients cannot be overemphasized. Yet in our island the difficulties in managing cancer pain go beyond education of physicians and nurses. Instances of our local limitations are:

a) Methadone^{7, 8} is considered by many experts as the ideal agent for control of severe pain in cases of advanced malignancies. It can be taken orally and it's action lasts up to eight hours, which is twice that of other agents such as meperidine. Nevertheless our local laws make this medication unavailable to patients dying of cancer while making it easily available to the more gorgeous and exciting patients with drug addiction.

b) The scarcity of narcotic analgesics in our community drugstores is a frequent problem to ambulatory cancer patients. Fear of been a target for robbery and violence is one reason for pharmacists to avoid dealing with controlled substances. Theirs is a realistic, although grim, argument in view of the rampancy of crime in our society.

So, Dr. Ramírez Rivera faces physicians involved with care of cancer patients or involved in training of physicians who will care for such patients with the following realities:

a) The occasional improper use of unconventional cancer chemotherapy out of the investigational setting.
b) The inadequate treatment of pain in too many terminal cancer patients. The relatively recent technique of tumor cell culture with subsequent testing for sensitivity to potentially beneficious chemotherapy agents might be of great help in avoiding unnecessary chemo-

therapy in a near future. Along the same optimistic vein, many advances are been made in the knowledge of pain physiology and pharmacology that may make more efficient the control of pain in patients with advanced malignancies. An interesting review on the psychoanalistic aspects of severe pain and the interaction between patient and physician has recently been published.⁶

Finally, it is in our hands to educate ourselves and our trainees in the art and science of pain releiving. It is also our duty to ilustrate our lawmakers on the necessities of our cancer patients.

Josi a. Lgola Roman M. D.

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PATHOLOGYReview

María Castillo-Staab, M.D.

Un hombre de 54 años con historial de hipertensión arterial, cálculos renales y dolores articulares desarolló una pequeña masa firme y dolorosa en el área del codo derecho.

La biopsia de la lesión reveló los cambios histológicos que aparecen en la figura 1.

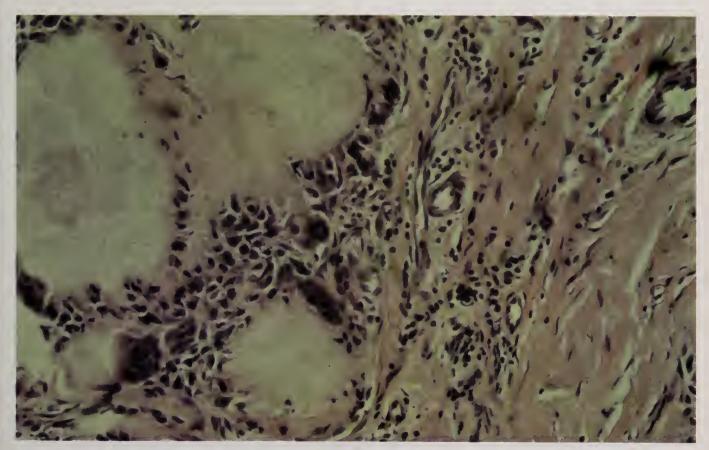


Figura 1. Sección histológica de la masa en el lado derecho

¿Cuál es su diagnóstico?

- A. Artritis reumatoidea
- B. Nódulo gotoso (tofo)
- C. Osteoartritis
- D. Sinositis villosa nodular
- E. Fiebre reumática, nódulo de Aschoff

Departamento de Patología, Escuela de Medicina, Universidad de Puerto Rico, Río Piedras, Puerto Rico

Nódulo gotoso (tofo)

El tofo es la lesión patognomónica de la gota. La gota es una enfermedad familiar degenerativa - inflamatoria relacionada a un trastorno en el metabolismo de las purinas que produce hiperuricemia, depósito de cristales de urato en los tejidos (tofos) y episodios repetidos de artritis.

Hay dos variantes clínicos importantes clasificadas como gota primaria y secundaria. En raros casos de gota primaria hay un aumento en la producción de ácido úrico por ausencia de la enzima hipoxantina - guanina fosforileosil transferasa que controla la biosíntesis de las purinas. El defecto genético se desconoce en la mayoría de los casos. En los pacientes que presentan gota secundaria la producción excesiva de ácido úrico se deriva de un aumento en el catabalismo de las purinas o disminución en la excreción. Se asocia con la administración de drogas que interfieren con la excreción de las uratas, fallo renal crónico, obesidad y ciertas dietas.

La gota primaria afecta más comunmente a hombres (95%) de edad mediana o a mujeres post-menopausicas. Se caracteriza por manifestaciones clínicas articulares agudas y crónicas. Los episodios agudos ocurren abruptamente y se acompañan de fiebre y cambios inflamatorios intensos a nivel de una articulación, siendo las más típica la articulación metatarsofalángica del dedo gordo del pie. Otras articulaciones frecuentemente afectadas son las del tobillo, muñeca, codo, pies y manos.

Las manifestaciones clínicas de artritis gotosa crónica son usualmente poliarticulares con daño y deformidad permanente de las articulaciones, usualmente acompañadas de depósitos de cristales de urato de sodio en los tejidos. La formación de tofos aumenta con la severidad de la hiperuricemia y de su duración.

Los tofos ocurren en las bursas arteriales, el cartílago de las orejas, tendones, cartílagos y huesos articulares y en el tejido blando alrededor de las articulaciones.

Histológicamente el tofo (Fig. 1) consiste en una masa de cristales de urato cristalinos o amorfas rodeadas por una intensa reacción inflamatoria compuesta por macrófagos, linfocitos, fibroblastos y células gigantes de tipo cuerpo extraño.

Diez a 20% de los pacientes con gota desarrollan cálculos renales y entre un 20 a un 40% presentan enfermedad renal. Estos pacientes presentan también hipertensión arterial.

Es importante recordar que la presencia de hiperuricemia (niveles de ácido úrico mayores de 7 mg/dl) aislada no es sinónimo de gota, que es en realidad una enfermedad poco frecuente y multifactorial.

Las manifestaciones clínicas de la gota pueden confundirse con las de artritis reumatoidea, ya que también produce nódulos subcutáneos. Se debe recurrir a la biopsia y el diagnóstico histológico para diferenciar adecuadamente estas lesiones.

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The ARDMS Executive Board is composed of 8 physicians, I acoustical engineer, I vascular technologist, 12 sonographers and I consumer representative. The Executive Board develops policies for planning and implementing the examinations. Each specialty is represented by a physician and a registered sonographer technologist engaged in the practive of clinical or academic ultrasound.

Examinations are administered annually in the United States, Canada and Puerto Rico under the direct supervision of the ARDMS at 23 test sites. Organizers for the ARDMS ensure that examinations sites meet ARDMS standards of proctoring, quality of facilities, confidentiality of exams and administration of exams. Dr. Edda C. Quintero has served as organizer for the test center in Puerto Rico since 1980. A test center will be available this year at the Veterans Administration Hospital, once more.

There are several stipulated pre-requisites in order to be eligible to take the Registry exam. The next Registry Examination is scheduled for October 19 and 20, 1985. Applications of this examination will be available form ARDMS Central Office in January 1985.

As organizers for ARDMS Test Center in Puerto Rico we urge all practicing sonographers to request information and application to ARDMS central office by filling and mailing the following request:

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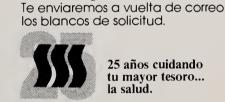
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Current medication brought blood pressure from 172/110 to 148/92 mmHg.

Family man

Loves kids...his wife would like several more.

Successful

Too preoccupied on business trips to remember his pills.

Impotent

Blames his current blood pressure medication.

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Manuel G represents 5,314 men age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Sexual dysfunction rare

Only 0.4% of the patients in the evaluation reported sexual performance problems²—making TENORMIN an excellent choice for men like Manuel G, who may have become impotent on other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Manuel G...and virtually all your hypertensive patients

TENORMIN® (atendal)



For Manuel G. and virtually all your hypertensive patients TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-{2°-hydroxy-3°-(1-methylethyl) amino] propoxy}- Atenolol (free base) has a molecular weight of 266 ft its a relatively polar hydrophilic compound with a water solubility of 26 5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23 it is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chlorotorm (3 mg/ml at 25°C) INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension it may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-lyne diuretic.

thiazide-type diuretic

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater
than first degree, cardiogenic shock, and overt cardiac tailure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory
tunction in congestive heart failure, and beta blockade carries the potential hazard of further
depressing myocardial contractility and precipitating more severe failure. In hypertensive patients
who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be
administered cauliously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with
beta blocking agents cure a period of times can be compaged, lead to acquired to the ret.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac tailure At the first sign or symptom of impending cardiac tailure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. It cardiac failure continues, despite adequate digitalization and diuretic. TENORMINI therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial inflarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it with-drawal symptoms occur.

drawal symptoms occur
Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta, "stimulating agent (bronchodilator) made available. If dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood
levels.

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and tinchloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg., dobutamine or isoproterenol with caution—see OVERDOSAGE). Mantestations of excessive vagal tone (eg., profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyrotoxicosis may be used with caution in patients with PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impared renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg., reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or posturial hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clondine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing dura tion of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding

Fertility of male or temale rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by a tenolol administration. **Animal Toxicology:** Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenololikg/day (150 and 75 times the maximum recommended human dose).

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo / letal resorptions in rats at doses equal to or greater than 50 mg / kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
nr abbits, the compound was not evaluated in rabbits at doses above 25 mg / kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justities the
potential risk to the tetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since
most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving
atenological.

afety and effectiveness in children have not been established

Pediatric Use: Salety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg., by checklist—toreign studies). The reported frequency of eli-cited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S.

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM: NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0.9%), nausea (4%-1%)
RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARPIOVASCULAR: headers and control of the production of the

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0-2%), light-headedness (3%-0-7%), tiredness (26%-13%), tatigue (6%-5%), lethargy (3%-0-7%), drowsiness (2%-0-5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenoiol)

TENORMIN (atenoiol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per

place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per formance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has colored with TENORMIN during investigational use and toreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension bronchospasm, and hypoglycemia

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted

Brandcardia: Atropine or another anticholinergic drug

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nor
epinephrine may be useful in addition to atropine and digitalis

Bronchospasm: Aminophylline, isoproterenol, or atropine

Bronchospasm: Aminophylline, isoproterenol, or atropine Hypoglycemia: Intravenous glucose.
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance talls below 35 ml. min 173 m² (normal range is 100-150 ml/min 173 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min 173 m²)		Atenolol Elimination Half-lite (hrs)	Maximum Dosage	
15-35		16-27	50 mg daily	
<15		>27	50 mg every other da	

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolo) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat light, and moisture. Store unit-dose and calendar packages at controlled from the store of the s

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room

References: 1. Data on file, Stuart Pharmaceuticals 2. Herman RL, Lamdin E, Fischetti JL, Ko HK-Postmarketing evaluation of attenolol (Tenormin*) A new cardioselective beta-blocker. *Curr Ther* Res 1983, 33(1) 165-171 3. Zacharias FJ. Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980; 6 (suppl 1):86-89



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ESTUDIOS CLINICOS

Right Ventricular Outflow Tract Reconstruction with the Revuelta Monocusp Patch

Raúl García-Rinaldi, M.D., Ph.D., FACS J.M. Revuelta, M.D., Ph.D. Katherine Poeppel PA-C Sanford Lubetkin, M.D. Carlos N. Monarrez, M.D., FACC

The surgical treatment of congenital heart diseases with obstruction of the right ventricular outflow tract requires enlargement of the pulmonary infundibulum, the valve annulus, and the pulmonary artery with a patch.^{1, 5} In extreme cases of pulmonary obstruction such as pulmonary atresia, valved conduits may be required for complete repair.^{2, 6, 14}

When a patch is required, pulmonary valve insufficiency usually results, affecting the function of the right ventricle on a short and long time basis. Consequently, the quality of life of such a patient with pulmonary insufficiency is sometimes markedly impaired. The detrimental long term effects of pulmonary insufficiency are evidenced by impaired cardiac reserve observed in these patients. 4, 8, 10

Based on the excellent results previously encountered with the Revuelta Monocusp Patch *in vitro* and *in vivo* we corrected a patient with a Pentalogy of Fallot with severe obstruction of the right ventricular outflow tract utilizing this bioprosthesis.³ This report summarizes, his pre, intra, and postoperative course.

Case Report

A fourteen year old male presented to the Memorial Hospital after having undergone cardiac catheterization in his hometown. This child, the product of an uncomplicated pregnancy and delivery, was cyanotic at birth. Due to socio-economic reasons the patient had not been subjected to intensive cardiologic evaluation or referred for surgical treatment earlier in life. The patient underwent cardiac catheterization and biventriculography, which revealed the presence of an atrial septal defect, a large ventricular septal defect (Fig. 1), a non atretic right ventricular outflow tract (Fig. 2), a dysplastic markedly



Figure 1. Right ventriculogram: There is marked trabeculation of the right ventricle. The ascending aorta and pulmonary arteries opacify simultaneously.



Figure 2. Right ventriculogram: The right ventricular outflow tract is not attetic although stenotic.

From the Surgical Service, Memorial Hospital, Houston, Texas and The Heart Clinic, Harlingen, Texas

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narrowed pulmonary valve and a small but patent pulmonary artery trunk that led distally to normal caliber right and left pulmonary arteries (Fig. 3). Oxygen saturations demonstrated a right to left shunt at the ventricular level. Mild aortic and tricuspid valve insufficiency were noted. The pressure in the right and left ventricles were identical (120/6). The systolic gradient across the pulmonary valve was 105 mm Hg (Table I). The diagnosis of severe Tetralogy of Fallot with an associated atrial septal defect (ASD) was made and the patient referred for surgical correction.



Figure 3. Pulmonary arteriogram: The dysplastic, narrowed pulmonary valve is noted. The right and left pulmonary arteries are of normal size.

Table I - Cardiac Catheterization

	PRE-OP		POS	OST OP	
Site	0 ₂ sat. (%)	Pressure (mm. Hg)	0 ₂ sat.	Pressure (mm. Hg)	
SVC	74				
RA	77	a = 11 $v = 8$ $m = 6$	67	a = 4 $v = 4$ $m = 2$	
RV	74	120/5	71	54/2	
RVO	74	120/5			
MPA	74	15/5 $m = 6$	74	$\frac{36}{12}$ m = 18	
RPA	72	15/5 $m = 6$			
LA	99	a = 11 v = 7 m = 8			
LV	93	120/5			
Aorta	84	m = 100			
Qp/Qs	.42				

RVO - Right Ventricle Outflow

MPA - Main Pulmonary Artery

RPA - Right Pulmonary Artery

LA - Left Atrium

LV - Left Ventricle

Qp/Qs - Pulmonary flow index/systemic flow index ratio

The patient underwent correction using total cardio-pulmonary bypass, and moderate systemic hypothermia (30°C). Bicaval and ascending aortic cannulation were performed using the techniques previously described. A sump was inserted into the left atrium via the right superior pulmonary vein. The right ventricular outflow tract was opened longitudinally across the pulmonary valve through the pulmonary annulus and into the distal pulmonary artery. An infundibular resection was then carried out by excising the septal band, and the parietal band and superficially resecting the crista supraventricularis. A large ventricular septal defect was closed with a double velour Dacron® patch using continuous monofilament 4-0 sutures. The closure was reinforced at the portion of the crista supraventricularis.

A monocusp patch of appropriate size (20 mm) was selected. Stay sutures were placed exactly at the point of insertion of the remaining cusp tissue of the native pulmonary valve to align the commissures of the prosthetic cusp (Fig. 4). The patch was anastomosed using the "open" technique to avoid accidental closure or narrowing of the distal pulmonary artery. The anastomosis was continued over the right ventricle on each side. When completed, blood was allowed into the right ventricle and hemostasis was accomplished. Since the patch was made of bovine pericardium no bleeding was

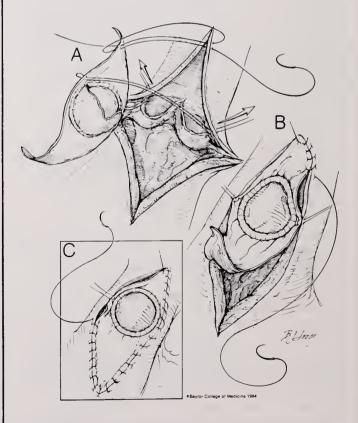


Figure 4. The right ventricular outflow tract and distal pulmonary artery were opened. The VSD was closed with a Dacron® patch and the septal band resected to relieve infundibular stenosis. The monocusp patch is positioned with the use of stay sutures. The patch is anastomosed with 5-0 polypropylene sutures, using the "open" technique.

observed. (Fig. 5) A vertical right atriotomy was performed. The atrial septal defect was identified and closed with a double velour Dacron® patch again using a continuous 4-0 monofilament suture. Upon completion of the repair spontaneous normal sinus rhythm ensued and the patient was immediately weaned from cardio-pulmonary bypass.

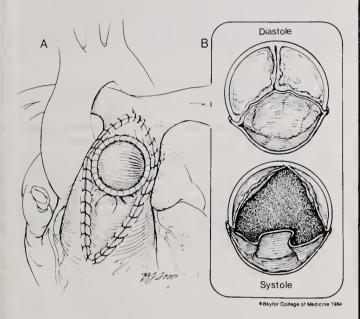


Figure 5. - A. Completed Repair. The Monucusp is supported externally by a plastic ring to prevent it from collapsing.

B. Diagrammatic representation of the function of the monocusp patch in

B. Diagrammatic representation of the function of the monocusp patch in diastole and systole. The monocusp abuts the remaining portions of the dysplastic pulmonary cusps.

The postoperative period was completely uneventful. The patient underwent right heart catheterization and right ventriculography eight days after surgery. The study revealed full pulmonary valvular competency, with a 22 mm Hg gradient across the pulmonary infundibulum. The right ventricular pressure was 56/4 and the pulmonary artery pressure was 34/10. Oxygen saturation demonstrated no stepup at the atrial or ventricular level. The patient was discharged, asymptomatic, on the 12th postoperative day.

Six weeks after surgery the patient was re-evaluated and had evidence of a post pericardiotomy syndrome. He was placed on an intensive regimen of aspirin, prednisone, and subsequently underwent pericardiocentesis. Also at that time, a holosystolic murmur suggestive of a residual ventricular septal defect (VSD) was noted although no VSD was detectable by echocardiography.

There was no pulmonary congestion. The patient resolved the pericarditis and now is asymptomatic five months after surgery. He is back in school although exhaustive exercise has been withheld.

Discussion

In 1964 Lillehei¹¹ first utilized a Dacron® monocusp patch for the reconstruction of the outflow tract in a patient with Tetralogy of Fallot. His technique was quickly abandoned because of the rapid thrombosis of the Dacron® valve.

In 1967 Marchand approached the problem of pulmonary insufficiency by implanting an aortic homograft. The technique was successful and became quite popular. Later it was noted that the aortic homograft would degenerate or calcify shortly after implantation. 9,17 In Japan, a similar implantation technique using a pulmonary artery homograft was utilized with equally discouraging results. In the last ten years monocusp patches of various compositions have been tried (fascia lata, ⁷ autologous pericardium, ⁶ porcine pericardium, ³ or bovine pericardium). ⁸, ¹²

The previously described monocusp patches have failed principally because of defective anatomical design, materials employed in their manufacture, or technical errors of implantation.¹⁶

The studies that we have performed in pulse duplicators of the right ventricular outflow tract and also in experimental animals have conclusively demonstrated the fundamental role that the configuration of an anatomic sinus of Valsalva plays in the mechanism of opening and closing of the monocusp prosthesis. ¹⁶ The sinus of Valsalva facilitates continuous washing of the valve during systole and diastole thus preventing the deposition of fibrin and other cellular elements that predispose to thrombosis, fibrosis, and/or malfunction of the monocusp valve. The design parameters of the Revuelta monocusp prosthesis were derived from an anatomical comparative study of the human pulmonary valve.

The long term evaluation (5 years) in animals as well as in humans has demonstrated that use of this bioprosthesis insures competency of the pulmonary valve after reconstruction of the right ventricular outflow tract. The factors that determine competency of the pulmonary valve are: correct size of the monocusp patch and correct implantation of the patch with alignment of prosthetic and native pulmonary cusp tissue.

Pulmonary competence then stays the progression of right ventricular dilatation. This is of particular importance in the immediate postoperative course and very important in the long term prognosis of these patients. Patients with this bioprosthetic monocusp demonstrate excellent exercise tolerance. Experimental and clinical study¹⁶ conclusively supports its use in correction of congenital anomalies requiring reconstruction of the right ventricular outflow tract.

Resumen: El tratamiento de las cardiopatías congénitas con obstrucción del tracto de salida del ventrículo derecho requiere ensanchamiento del infundibulo pulmonar, el anillo valvular y la arteria pulmonar con un parche. Como se ha demostrado que la insuficiencia pulmonar no es deseable, se diseñó un parche con una válvula monocúspide para el tratamiento de estas cardiopatías. Este trabajo resume el curso de un paciente con una Pentalogía de Fallot, tratado con esta prótesis.

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Attitudes Toward Post-Mastectomy Reconstruction in Puerto Rico

Rita Laracuente, M.D. Norma I. Cruz, M.D.

Summary: Using a sample population of post-mastectomy patients obtained from the Puerto Rico Cancer Register files, the attitudes toward reconstructive breast surgery after mastectomy were evaluated.

We found that 60% of the women interviewed wanted to have a reconstructive mammoplasty, being only in the group over 60 years of age that lack of interest occurred.

Information regarding reconstruction was obtained by 24% of the patients from their general surgeon and of these group only 1% was referred to a plastic surgeon.

One percent of the total group interviewed had undergone some form of breast reconstruction.

The rehabilitation of women who are subjected to mastectomy for breast cancer has only recently been given the importance it deserves.

Generally, the psychological process attending mastectomy is characterized by a depressive reaction, a sense of mutilation and a loss of feelings of femininity. Besides the altered body image, the patient also faces the fears of recurrence of her disease and death. The high incidence of breast cancer which currently affects one out of every eleven women, makes post-mastectomy rehabilitation a problem of significant magnitude.

In an effort to establish a program to help the mastectomy patients regain their body image and feelings of sexual attractiveness, we explored the attitudes toward post-mastectomy reconstruction in a sample population obtained through the Puerto Rico Cancer Register files.

Material and Methods

The records of 110 live women who had undergone mastectomy for breast cancer in the past 5 years were obtained from the Puerto Rico Cancer Register files. Letters were sent to all these patients requesting their assistance to an evaluation interview at the University of Puerto Rico School of Medicine. If the patient was unable

to come to our office a telephone interview was considered acceptable.

A questionnaire was filled requesting the following information:

- 1) age
- 2) type of mastectomy
- 3) whether reconstruction was requested or desired
- 4) whether the surgeon had spoken to the patient about reconstruction.
- 5) whether the patient would be willing to pay for the surgery.
- 6) marital status
- 7) whether loss of spouse occurred after mastectomy.

Only 45 patients responded to the letters and they provided the requested information by telephone or personally.

Results

The sample population of 45 women who had undergone mastectomy for breast cancer was broken down according to age groups as follows:

age interval	number of patients
30-39 years	10
40-49 "	12
50-59 "	15
over 60 years	8
	45 total

A total of 36 of these patients had undergone a modified radical mastectomy with preservation of the pectoralis major muscle and only 9 patients had been managed with a standard radical mastectomy. All patients had stage I (70%) or II (30%) disease.

When questioned about their desire to have breast reconstruction, 60% of the group replied that they were interested in reconstructive surgery. The results were tabulated according to age intervals as follows:

age interval	patients interested in reconstruction		patients that had reconstruction	
30-39 years	7/10	(70%)	2	
40-49 years		(83%)	1	
50-59 years		(53%)	1	
over 60 years	2/8	(25%)	0	
total group	26/45	(60%)	4/45 (1%)	

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^{*}Medical insurance companies in Puerto Rico, such as SSS and Cruz Azul do not cover post-mastectomy reconstruction.

Patient over 60 years of age ga. responses significantly different (p value less than 003) from the group as a whole. Women in this older age group viewed breast reconstruction as not necessary to an improved body image, unless the contralateral breast was very large creating a noticeable asymmetry problem.

It was found that only 24% (11/45) of the general surgeons performing the mastectomies had explained to their patients about the possibility of breast reconstruction.

Of the patients that were interested in reconstructive surgery 76% were willing to pay for this procedure, the others would have the proce are only if their medical insurance would cover such service.*

Marital status of the group was as follows:

married	unmarried
30 (67%)	15 (33%)

Loss of spouse occurred in 13% (4/30) of the group after the mastectomy, which appeared to have been a contributory factor in the separation.

Discussion

Psychological assessments of the patient acceptance of mastectomy without reconstruction have been reported in the literature to be higher in older age groups.³, ⁴ This finding appears to be similar in the Puerto Rican population where patients over 60 years of age seldom requested reconstructive surgery unless a contralateral large and ptotic breast created significant asymmetry, difficult to balance with an external prosthesis.

The younger groups on the other hand have a high nonacceptance of the breast loss and part of their rehabilitation should include reconstructive breast surgery to help them regain a sense of wholeness in their body image.

Lack of medical information as to the possibility of reconstruction and the various alternatives was found to be common in our sample population. Only 24% of the patients received information from their general surgeons regarding reconstruction and only 4 patients (1%) were referred to plastic surgeons. The fact that only 4 out of 45 patients had breast reconstruction is difficult to evaluate since financial limitations play an important role in Puerto Rico were the most common medical insurance carriers do not cover post-mastectomy reconstruction.

Spouse loss being a multifactorial problem is also difficult to evaluate but the lowered self-esteem and the notion of being viewed as less feminine was brought up as a significant factor in post-mastectomy separations.

In summary this study confirms that a need exists in the younger post-mastectomy patients for breast reconstruction as part of her total rehabilitation. It would also appear that the general surgeon should assume a more active role providing information on the alternatives available in reconstructive mammoplasty.

Resumen: Usando una muestra poblacional de pacientes con mastectomías, obtenida de los archivos del Registro de Cáncer de Puerto Rico, se evaluaron las actitudes hacia reconstrucción de seno.

El estudio reveló que 60% de las mujeres deseaban una mamoplastía reconstructiva, siendo solo en el grupo mayor de 60 años de edad que se encontró falta de interés por esta modalidad de reconstrucción.

Información relacionada con alternativas de reconstrucción de seno después de la mastectomía se le había ofrecido a solo 24% de las pacientes por el cirujano general y de éstas pacientes solo 1% fueron referidas a un cirujano plástico.

Del total de pacientes entrevistados 1% había tenido alguna cirugía reconstructiva después de su mastectomía.

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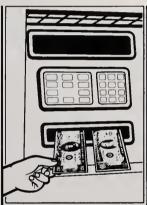
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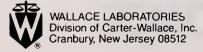
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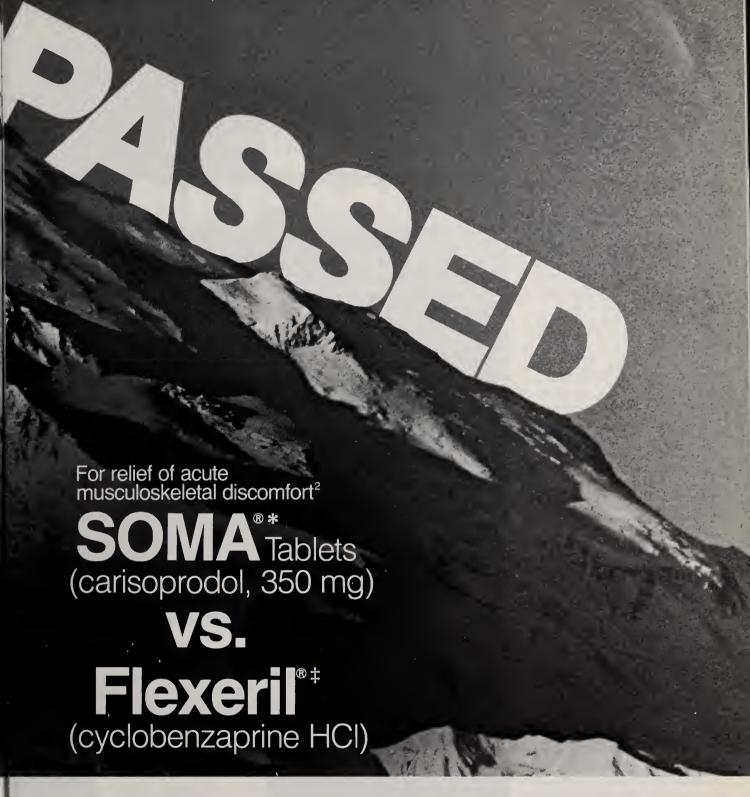
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- Flexeril had a statistically significant higher incidence of dry mouth (p≤0.05).

As Soma relieves muscle spasm, activity impairment diminishes and patients are often able to resume more normal activities.

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- *As an adjunct to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.
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Soma 8 (carisoprodol)

Before prescribing 'Soma', consult package circular or latest PDR information, a brief

summary of which follows:

INDICATIONS: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS: Porphyria; allergy or idiosyncrasy to carisoprodol or related compounds such as meprobamate, mebutamate, or

tvbamate

WARNINGS: Idiosyncratic Reactions: have appeared very rarely within minutes or hours after the first dose of carisoprodol. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation. Symptoms usually subside in several hours, but supportive and symptomatic therapy, including hospitalization, may be necessary.

Pregnancy and Lactation: Safe use has not been established; weigh potential benefits against potential hazards during pregnancy and lactation or in women of childbearing potential. Usage in Children: 'Soma' - Not recommended

under age 12.

Potentially Hazardous Tasks: Caution patients against engaging in potentially hazardous activities requiring complete mental alertness (e.g., driving, operating machinery).

Additive Effects: Effects of carisoprodol with alcohol, barbiturates or other CNS depressants or psychotropic drugs may be additive. Drug Dependence: Use caution in addictionprone patients

PRECAUTIONS: Administer cautiously to patients with compromised liver or kidney function to avoid excessive accumulation of cariso-

ADVERSE REACTIONS: Drowsiness or other CNS effects may require dosage reduction. Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, tachycardia, postural hypotension, facial flushing, nausea, vomiting, hiccup and epigastric distress have been reported. Pancytopenia (attributed to phenylbutazone) and leukopenia (in combination with other drugs or viral infections) were reported in isolated instances. Allergic or idiosyncratic reactions have occurred occasionally after the first to fourth dose (see "Warnings"). In such cases, discontinue the drug and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids). These reactions include: rash, erythema multiforme, pruritus, eosinophilia and fixed drug eruption. Severe reactions included asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock

DOSAGE AND ADMINISTRATION: Adults -One 350 mg tablet 3 times daily and at bedtime. OVERDOSAGE: Has produced stupor, coma, shock, respiratory depression, and very rarely death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, monitor blood pressure, respiration, cardiac status and urinary output; use symptomatic and supportive measures. Avoid overhydration. Relapse due to incomplete gastric emptying and delayed absorption has occurred. Peritoneal and hemodialysis and diuresis have been used success-

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ARTICULOS ESPECIALES

First Relieve Suffering

José Ramírez-Rivera, M.D., F.A.C.P.*

Medical training has given little emphasis to Abstract: tailoring diagnostic efforts and treatment to the individual circumstances of patients. Physicians are more concerned with artful therapeutic intervention to control disease than with the restoration of existential function to their patients. Three standard textbooks of internal medicine and three practical manuals in common use provide meager information about the supportive care of the dying. Cytotoxic agents are used without regarding their impact on the quality of life of those receiving them. Pain is improperly gauged and poorly managed by health professionals. Physicians are reminded that their goal is to care for people, not simply to fix misbehaving organ systems. To do this, particularly with the terminally ill, they must first relieve suffering.

In recent years a growing awareness has developed that our responsibility with patients, fellow human beings, requires more concern about relieving suffering and less about prolonging life.¹⁻⁴ In medical training, however, the emphasis continues to be placed on the simpler task of taking all the right steps to make an accurate diagnosis and delivering the corresponding treatment. The judgmentally more difficult undertaking of making diagnoses accurate enough for the circumstance of the individual patient (and of recommending a treatment appropriate to this diagnosis and this circumstance) is usually not encouraged. Such an undertaking requires at least an overview of the patient's personal goals, an appraisal which in many busy medical practices seems to be habitually ignored.

When life is threatened, before we embark on the frequently tormenting and fantastic voyage simplistically called diagnosis and treatment, assessment of each individual's goals becomes necessary. We are fairly certain that a patient who seeks our help wants to have health restored. But, if restoration of health is not

attainable, what other goals are there? It is clear that one human being may not necessarily want deforming surgery or a torturous hospitalization; another may reject squandering the economic resources he has gathered throughot his lifetime in order to attain a few more months of marginal and painful survival.

The fundamental difference between man and beast becomes blurred when we consistently orient our therapeutic goals towards biological persistence rather than to restoration of existential function. Illness with its associated reactions —shame for being faulty, anxiety for ignoring outcome, depression and bitterness for not perceiving a gentle caring hand— needs more than an accurate diagnosis and a precise chemical formulation for cure. The return to wholeness is not an automatic result which follows the correction of misbehaving organ systems. It is a slower process that requires identification and fulfillment of needs; it demands constructive steps towards restoration of the self as it is perceived.

Suffering may occur at any age or under any circumstance when any aspect of the person is threatened, but nowhere is suffering more generally recognized than in the terminally ill. Our recently acquired capacity to maintain teetering biological functions by using complex medical technology and potent medications makes it imperative that we accept our share of responsibility for the quality of life of those who are about to die.

Most religious traditions teach that no absolute obligation exists on the part of the physician to use extraordinary means to preserve life; they profess that the infliction of unwarranted pain on ill and dying persons is immoral. Our society in general is reaching the same conclusions. ⁵⁻⁶ Although many physicians claim to subscribe to these tenets, their care of the terminally ill frequently does not show it. Their main interest seems to lie in artful therapeutic interventions to control disease. Meager attention is paid to the personal threat inherent in serious illness or to the consequences of crafty chemical and physical manipulations on the integrity of the person. They seem to view the relief of suffering as a second rate side show.

In the cytotoxic chemotherapy of solid tumors, for example, meticulous measurements of tumor shrinkage are performed and prolongations of life for a few weeks

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are dramatically announced. But few study protocols include measurements of subjective toxicity or assessments of the impact of treatment on the quality of life. About 4 percent of advanced or inoperable cancers are potentially curable by differential poisoning; life is prolonged in less than 20 percent.⁷ Should we not weigh in a more humane scale the effectiveness of cytotoxic chemotherapy?⁸

A lack of interest in the compassionate care of the dying is demonstrated in recent editions of three standard textbooks of internal medicine. 9-11 I have reviewed the following topics in each: terminal illness, dying patients, treatment of metastatic cancer, analgesics, narcotics, pain relief, intractable pain. Only 12 of the 6,521 pages of written text were dedicated to these important topics. Four practical manuals commonly used by housestaff in three different disciplines were similarly surveryed. 12-15 The concept of supportive care for the terminally ill was alloted not more than a page in three of them; 12-14 in none were specific details given on the proper use of narcotic analgesics. By way of contrast, the somber tales of the currently glamorous, but much less common, narcotic abuse and its consequences were more amply presented.

Little is being done in medical texts or the current literature to correct the rampant misconceptions about pain and its management. Perphaps the facts about endorphins are beginning to root out the mistaken notion that people who respond to placebos have no "physical" pain. Yet, the practice persists of prescribing "the standard dose" of narcotic analgesics to be given "as required" rather than establishing by titration how much analgesic is needed and scheduling the next dose *before* the previous dose has fully worn off.¹⁶

Knowledgable nurses are caught in the uncomfortable predicament of having to follow physician's orders for relief of pain with the complete certainty that the amount of analgesic ordered is woefully inadequate.^{17, 18} These nurses know that the analgesic requirements of different painful conditions vary, that patients with the same condition may also have different pain perceptions. They seem to be better acquainted than many physicians with the parenteral doses of narcotics and their oral equivalents (Table I). They are fully aware, for example, that 2 aspirins and 30 mg of codeine by mouth relieve pain better than the commonly prescribed dose of 50 mg of intramuscular demerol.

The inadequate management of pain can be improved. To elicit more effective prescriptions, health professionals are using rating scales to quantitate, on an hourly basis, the severity of the pain and the effectiveness of its relief.18 The pain intensity may be rated on a scale from 0 to 5 in this manner: 0 = none, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, 5 = excruciating¹⁸ and the relief can be rated as minimal, substantial. or complete. The informed nurse can then call the physician in these terms: "In the last two hours your patient has had nearly as much pain as when he received the 50 mg. of intramuscular demerol you ordered. Can we increase the dose to 75 mg, every three hours beginning now?" In sophisticated settings nurses have wrested the management of pain from the faltering hands of physicians with flexible orders such as this one: "50-100 mg of demerol by mouth or intramuscularly every 3-4 hours as required." They have favored prescription of oral narcotics for chronic pain in order to facilitate the task of providing effective analgesia in the hospital and later at home.

When ignorance prevails, physicians and nurses report to each other with enthusiasm their success in prolonging the time between narcotic injections or the effectiveness of a placebo in severe chronic pain. They do not seem to know that lower total doses of analgesics are required when one responds promptly to patient's needs. They are tragically unaware that in effective pain management, and particularly for the terminally ill, there are no maximum doses of analgesics. ²⁰ It is doubtful that these uniformed physicians or nurses will offer the dying the skillful blend of personal support, anxiolytics, and analgesics required to fulfill their professional calling.

We have each a personal past and cultural background that strengthen or weakens us in an encounter with adversity. Each human being has his place in the sun, his responsibilities and privileges. More than physical agony it is the limitation, the distortion of each one's unique functioning image, that causes suffering. The exaggerated orientation to the somatic and the measurable in our scientific age neglects the fact that a sick man—unscientific and unmeasurable, a learned animal— is not simply an aggregate of organs in varying stages of disarray. He is a human being capable of personal unique and profound suffering. If our purpose as physicians is to care for people—not to fix organ systems— if we mean to

TABLE I

NAME	TRADE NAME	DOSE (mg)		DURATION OF ACTION	
		Parenteral	Oral	Hours	
Morphine		10	60*	4 - 5	
Codeine		120*	200*	4 - 6	
Hydromorphone	Dilaudid	1.5	7.5	4 - 5	
Oxycodone	Percodan	10-15	30*	4 - 5	
Levorphanol	Levodromoran	2-3	4	4 - 5	
Methadone	Dolophine	7.5-10	15	3 - 5	
Meperidine	Demerol	80-100	300*	2 - 4	
Pentazocine	Talwin	60*	180*	3 - 4	

^{*}These doses are higher than are usually prescribed or recommended for this narcotic.

restore existential function to the terminally ill, we must not fall into the primitive trap of merely abetting biological persistence. We must care for the person. To care for humans effectively we must first relieve suffering.

En la educación médica se le ha dado poca Resumen: importancia a ajustar los estudios de diagnóstico y los esfuerzos terapeúticos a las circunstancias del paciente. Los médicos están más interesados en ingeniosas intervenciones terapeúticas para controlar enfermedades que en la restauración de la función existencial de sus pacientes. Tres libros de texto de medicina y tres manuales prácticos de uso común proveen información exigua sobre el tratamiento de sostén del paciente condenado a morir. Se usan agentes citotóxicos sin tener en cuenta su impacto en la calidad de vida de aquellos que los reciben. Los profesionales de la salud miden mal la intensidad del dolor y lo tratan inefectivamente. Se le recuerda al médico que su meta principal es atender pacientes, no componer órganos en desarreglo. Para hacer esto, particularmente con pacientes mortalmente enfermos, primero hay que aliviar el sufrimiento.

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Presentación de Casos

Amniotic Band Related Compression Defects

Antonio Pou-Martínez, M.D.

With more frequent sonographic evaluations being performed on pregnant female patients for diverse reasons, three things will invariably happen; more sophisticated equipment will develop, interpretative skills will improve, and subtle anomalies will be diagnosed earlier in gestation. This report presents a patient who had ultrasonographic prenatal diagnosis of a significant amniotic band that resulted in a term delivery with evidence of compression-induced anatomic abnormality.

Case Report

A 32 year old female, a gravida 3, paral, abortus 1, presented for prenatal care a 6 weeks by size and dates. At that time she had mild bleeding and was ordered bedrest and did well. At 14 weeks gestation a sonogram was ordered because of mild size-dates discrepancy and a normal single pregnancy consistent with 12 weeks was found. At 24 weeks gestation by dates the patient again bled and repeat sonogram showed anterior-posterior placenta, no fetal anomalies, a transverse-variable lie, and an amniotic band in the upper right fundal portion of the uterus, which seemed separate from the fetal parts (Figure 1). The biparietal diameter was equivalent to 25 weeks and the amount of amniotic fluid was increased. Subsequent sonograms done at 28 and 29 weeks gestation repeatedly showed the amniotic band (Figure 2).

The patient was delivered vaginally at 42 weeks gestation by dates of a male who weighed 3119 grams with Apgar scores of 8 and 9. The placenta grossly revealed an amniotic band (Figure 3). The baby had the following findings attributed to the amniotic band: an assymetrical fascies, hypoplastic left mandibule, and indentations across the right forehead and also in the left temporal area (Figure 4). Radiological evaluation of the mandibules showed no fractures or bony defects.

Discussion

Amniotic bands can produce gross anomalies, many of which are amputations of arms and digits. Less severe abnormalities as the ones presented above can occur. The case presented shows the benign end of a continuum of



Figure 1. Sonogram at 24 weeks showing amniotic band.



Figure 2. Sonogram at 28-29 weeks showing amniotic band.

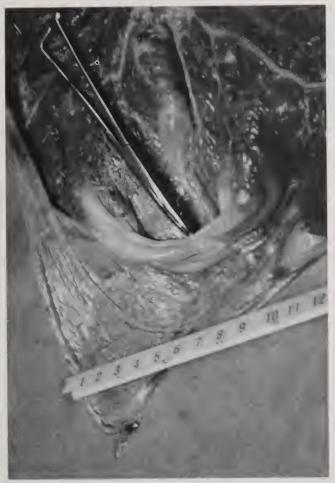


Figure 3. Placenta demonstrating thick amniotic band.



Figure 4. Newborn demostrating mild compression defects.

increasing severity of amniotic band effects.

Torpin,³ proposed that these deformities were secondary to early rupture of the amniotic sac. Miller et. al.,² mention that amniotic bands will cause defects by compression or by encircling, and that there is a spectrum going to limb-body wall deficiency as the most severe. Fiske,¹ states that sonographic diagnosis requires fetal parts on both sides of the membrane or band; but this could be true for major defects and not necessarily for minor compression defects as presented above.

It is recommended that upon sonographically visualizing an amniotic band, careful and frequent study of the whole fetus be undertaken to identify abnormalities. Individualization of each case is of utmost importance.

Resumen: Se presenta un caso en el cual se identifica sonográficamente una banda amniótica en diferentes edades gestacionales. Se identifica la misma en la placenta y se observa efecto de compresión en un bebe nacido a término.

Se demuestra que las bandas amnióticas pueden afectar a un feto en una manera leve.

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Sick Sinus Syndrome in an Adolescent and A Young Adult

Charles D. Johnson, M.D., FACC

The Sick Sinus Syndrome (SSS) has many etiologies. It is being recognized also in children, adolescents and young adults, secondary to a number of causes, of which the most frequent permanent cause in children is post-cardiac surgery for repair of transposition of the great arteries (TGA) and atrial septal defect (ASD).

These two cases emphasize the problem of the SSS in adolescence and young adulthood.

Case 1

This 16-year-old male demonstrated the clinical and catheterization findings of a primum ASD in early childhood. At age 5 1/2 years, a 2.5 cm defect was closed with continous silk suture, and right atrial purse-string, under pump oxygenator. About 18 and 41 days later, electrocardiograms (ECG) showed sinus bradycardia < 60 per minute and junctional escape beats (JEB). The rate rose to 80 on exercise. In later years the patient was asymptomatic and active, but there was cardiomegaly and sinus bradycardia (rate 40, 55) with JEBs. At age 16 he presented as a tall, lanky teenager with myopia and a hypoplastic kidney. He has been a asymptomatic and working.

Holter monitoring revealed a minimal heart rate of 13.9 per minute (pause of 4.32 S) while sleeping, but the heart rate rose to 141 during treadmill exercise.

Figure 1 shows primary extreme sinus bradycardia (rate < 22 per minute) -actually 2:1 sinoatrial (SA) blockwith a slow secondary atrioventricular (AV) junctional escape rhythm (JER), minimal rate <30, 2040 mS, retrograde atrial conduction producing reciprocal beats (RB) with slight phase 3 aberration and T wave change. and atrial fusion beats (R- $\acute{P} = \pm 0.47 \text{ S}$; $\acute{P} - R = 0.16 \text{ S}$) of AV junctional origin. Backward measurement of 2040 mS from the next JEB identifies the moment of its preceding discharge by the reciprocal impulse. The RB dislocates the junctional rhythm. The R - R cycle following the RB is shorter (concealed conduction). In the lower strips there is a long period of sinus and ventricular arrest/standstill -4320 mS, rate 13.9/min.- terminated by a sinus conducted beat (failure of junctional escape-sick AV junction).

Figure 2 shows an idiojunctional rhythm, rate 32-33, with variable retrograde atrial conduction, or Double Junctional Rhythm and atrioventricular dissociation (AVD). There were also: sinus arrhythmia, wandering atrial pacemaker to the AV junction, AVD, isorhythmic AVD, a JER with retrograde Wenckebach block,

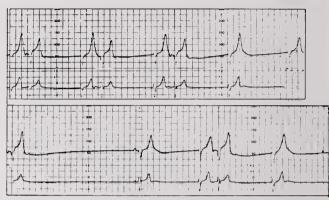


Figure 1



Figure 2

multifocal ventricular premature beats (VPB), interpolated with retrograde concealed conduction.

An Intermedics DVI 259-01 permanent pacemaker was implanted epicardially with a subcostal generator, and he has remained asymptomatic.

Case 2

This 23-year-old working male consulted a physician because of a productive cough and low abdominal pain. He was found to have "complete atrioventricular block." He gave a past history of mumps, measles and bronchial asthma; the family history was negative. He was considered to possibly have a viral myocarditis. His 12-lead and ambulatory ECGs revealed a heart rate ranging from 31 to 100 per minute.

Figure 3 demonstrates marked sinus bradycardia and arrhythmia, and sinus arrest- 2:1 SA block (the longest pause was 3132 mS, 19/min). There is ST segment elevation suggesting the Early Repolarization Syndrome, a normal variant.

Figure 4 shows two long pauses of 2800 mS and 2920 mS. There were also: SA block with JEBs, JEB with sinus capture, atrial premature beats (APB), VPBs, tachyarrhythmia, accelerated junctional rhythm, incomplete and isorhythmic AVD, sinus capture beats with left and right bundle branch block (BBB) patterns, a "Sluggish, Ailing" AV node and incomplete right BBB.

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A Medtronic 7000 DDD permanent pacemaker was implanted. Subsequently, abdominal pulsations ensued secondary to diaphragmatic stimulation from "phrenic nerve stimulation", solved by reducing the atrial pulse width from 0.5 to 0.2 mS. The patient is now working and asymptomatic.

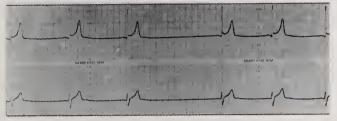


Figure 3

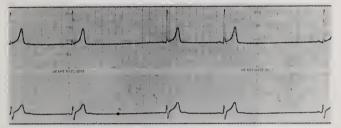


Figure 4

Discussion

There are numerous etiologies of the SSS. In young people, particularly, the following should be considered: congenital heart disease, viral myocarditis, cardiomyopathies, viral ganglionitis and infectious processes, appendicitis, Hirschprung's disease, antiarrhythmic drugs, enhanced vagotonia, absence of other heart disease, etc. Fatty infiltration, degeneration and fibrosis of the SA and AV nodes and atrial preferential pathways have been found at detailed cardiac autopsy examinations. SSS in the young can either be benign, or serious and fatal.

Sinus bradycardia and arrest, types I, II and complete SA block with junctional escape may occur in healthy asymptomatic, or symptomatic with syncope, young boys, as well as first degree AV block, APBs and VPBs. Minimal rates may be as low as 30/min during sleep and while awake. Electrophysiological studies (EPS) have demonstrated defects in automaticity and conduction. SA and AV nodal disease has been observed in athletic, tall large young males with a positive family history, perhaps on a genetic basis. James has shown the sinus node artery to be narrowed, with intimal and medial hyperplasia, nodal fibrosis and hemorrhage. Heart rates (sinus pauses) in the 30s have been found by Holter monitoring in normal medical students, and pauses > 2 S in athletes.

However, the most frequent permanent cause of sinus node dysfunction in children is surgical damage of the SA node, most frequently transpiring after repair of TGA (Mustards operation), ASDs (ostium secundum and

primum, sinus venosus) and the Fontan operation for tricuspid atresia. This occurs immediately in the postoperative period (75%), or years later. It has been ascribed to surgical damage of the node or its artery, or internodal atrial tracts, particularly after extensive atrial reconstructive surgery, caval intubation with right atrial dilatation, and atrial suturing. Examination has shown histological damage to the AV node, hemorrhage, necrosis, inflammation, foreign body reaction, thrombosis of the SA node artery and suture material in and about the SA node. In these cases tachy- and bradyarrhythmias (sinus bradycardia and arrest and SA block, asystole, nodal and ventricular escapes follow; in some cases junctional automaticity is depressed) have been observed. In SSS after Mustard or ASD repair AV conduction is usually normal, but is often damaged after other intracardiac repairs such as ostium primum and single atrium.

Moreover, SA and AV junctional dysfunction are frequent in ASD patients even presurgically. There is a recent report of the SSS, an ASD and congenital absence of the pericardium. Holter and EPS have revealed: first degree AV block, prolongation of internodal conduction time and AH interval (33%) and effective AV nodal refractory period, abnormal low rate at onset of AV Wenckebach block during atrial pacing, abnormal corrected sinus nodal recovery time (CSNRT), atrial flutter, ectopic atrial rhythms, junctional rhythm and tachycardia with reentry. This may be on an embryological or a hemodynamic basis (in the older patient, and in the presence of a larger left-to-right shunt). The combination of an ostium secundum ASD and abnormalities in AV nodal function have been reported in several members of th same family, suggesting an autosomal dominant pattern of inheritance.

Management

Careful attention to the anatomy of the SA node, its artery and internodal tracts during surgery may prevent the SSS.

The standard ECG, 24-hour Holter monitoring, stress ECG and cardiac EPS are diagnostically valuable.

Atropine IV (1-2 mg) may be useful prior to temporary pacemaker insertion. A permanent demand pacemaker is indicated, is safe and effective, if symptoms or syncope are present, if the escape rate is inadequate or there are tachy —or bradyarrhythmias persisting for more than a few weeks or requiring cardioversion or antiarrhythmic drugs. There is a growing number of children and young people who have received pacemakers— epicardial ventricular, atrial, AV sequential and universal; endocardial atrial and universal. An endocardial approach and physiological units are now favored.

Case 1 in this report was asymptomatic with a heart rate of 14/min. Marmor and Black have documented an asymtomatic/lethargic man with profound sinus bradycardia, etc, when asleep (11/min), and a sinus arrest of 5 1/2 S. Even a 15 S pause may not induce symptoms.

This communication documents two cases of severe SSS in young patients, and briefly reviews this increasingly recognized cardiological entity.

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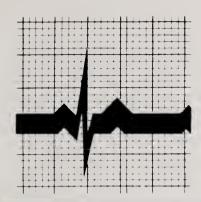
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ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, MD, FACC

Figure 1A is the electrocardiogram (ECG) and Figure 1B lead II and V₄R rhythm strips of a woman.

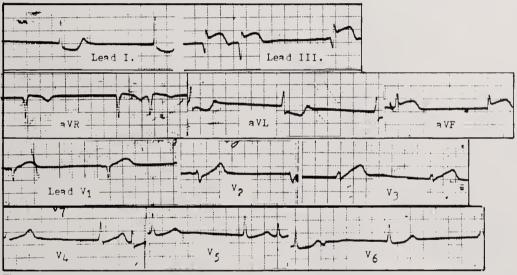
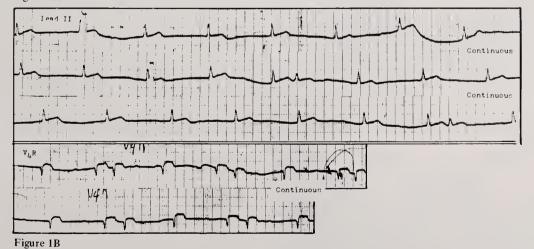


Figure 1A



Questions

- 1. What are the electrocardiographic diagnoses?
- 2. What is the diagnosis of the arrythmias?

Answers

Acute Inferior Myocardial Infarction (AIMI).

ST segment elevated in leads III and aVF; Qr in lead III, ST depressed in leads I, aVL, V_{5-6} .

Acute Right Ventricular Infarction (ARVI).

ST segments elevated in a VR, V_1 , V_4 R; QS in V_1 and V_4 R. Autopsy revealed anterior and posterior infarction and ARVI. A myocardial perforation was likely as 20 cc of blood was found in the pericardial cavity.

Atrioventricular dissociation, incomplete.

P-P cycle variable, the P and QRS rates are near 40-43/min. P waves are hardly visible at times, but may fall in the ST segment. Sinus capture of the ventriclesmay be characterized by first degree AV block, phase 3 aberration block, and perhaps in the supernormal period of AV conduction.

May be a form of the syndrome of 2:1 AV block with AV dissociation. In V_4R the junctional escape rate is near 50 (1200) mS), and the P rate may be 88/min. There is also 1200 mS between the capturing P wave and the next junctional escape beat. The capturing sinus impulse during its passage through the AV node, reaches the AV nodal pacemaker and discharges it prematurely - presets the AV nodal rhythm. At this moment, the AV cycle begins again. The postectopic cycle is equivalent to the normal AV nodal cycle.

Suggests 2:I sinoatrial block. Perhaps a blocked atrial premture beat in V_6 .

Sick Sinus Syndrome in AIMI. Possible atrial infarction.

Discussion

ARVI is a frequent concomitant (19-59%) of transmural AIMI and has recieved increasing attention in recent years. It has been considered difficult to diagnose by electrocardiography, perhaps because the RV mass is small in comparison to that of the left ventricle (LV), the Q wave may be obscured in V_{1-2} as the electrical wave front depolarizes the interventricular septum, and only diagnosable when clockwise rotation of the RV or major RV involvement are present.

The diagnosis of ARVI by ST segment elevation in procordial leads V_1 , V_4R and CR_4R , has been attempted in the past. ST segment elevation was suggested to be a sensitive and specific indicator of such in the presence of AIMI; if >1 mm, there was >24% likelihood of the infarct reaching the RV lateral free wall. ST segment elevation (0.5 mm or more above the isoelectric line) in the right precordial lead V_4R is a relatively sensitive (83%) and specific (77, 88%) sign with a predictive value of 70%. The sensitivity and predictive value are greatest for leads V_4R to V_6R . ST segment elevation of 0.1 mV or greater, in one or more leads V_4R , V_5R , V_6R , was both highly sensitive (90%) and specific (91%) in identifying ARVI. This lead combination was better than V_4R or any other single right precordial lead.

Another major study found that the presence of injury

and necrosis waves in V₄R or V₄R to V₃R during AIMI (all had ST segment elevation in leads II, III and aVF) was a useful criterion in that they insured a highly specific diagnosis of ARVI in the great majority (76 and 71%. respectively) of the cases with autopsy evidence of RV involvement. ST segment elevation of at least 0.05 mV and the morphology of the QRS in leads V₄R, V₃R and V¹ were accepted. QS, QS complexes or disappearance of R, in both V_AR were specific markers of ARVI, with a specificity of 100% and sensitivity of 78%. Normally, there is always a rS complex in V₃R and frequently in V₄R (91%); V₆R show rS, rSr, QR or QS (25% in V₆V, 10% in V_5R , 2.4% in V_4R) complexes. So, the RV cavity may manifest a QS rather than a rS complex. The ST segment change may be transient, disappearing within 2-10 hours of onset of the chest pain. There are also the accompanying signs of AIMI. ARVI may favor ventricular fibrillation during temporary pacing for bradyarrythmias complicating acute myocardial infarction (MI).

The pathogenesis of the ECG findings is not clear but has been attributed to, a) transmural RV damage, b) the associated infarction of the posterior interventricular septum and inferior RV reflected through necrotic and electrically silent RV myocardium, and c) the ST segment elevation represents the phase of RV transmural ischemia- ischemic injury.

Differential diagnosis comprises: 1) anteroseptal MI with ST elevation in lead V_1 , due to anterior ST vector deviation, 2) left bundle branch block, and other causes of anteriorly oriented ST vectors, 3) the degree of ST elevation depends upon the prominence of ST elevation in leads II, III and aVF, 4) a lateral MI could cancel the ST elevation, 5) septal MI; 6) the ST elevation was not observed in unstable angina pectoris nor in normal subjects.

This has proven a simple, early warning sign of ARVI, to anticipate, prevent and treat its complications of cardiogenic shock from extensive MI of the LV, and AV conduction blocks. Thus, necrosis of the RV free wall often is not silent by the ECG.

Recently, one study found ST segment elevation in V_{1-5} to occur in patients with ARVI, but this was not observed in another study, and was equivocally present in the described patient. This latter recently published study noted that patients with ST segment elevation of 1 mm or more in lead V_4R generally have a proximal (before the first RV branch) stenosis of the right coronary artery, and that this finding reliably identifies the group with depressed RV function which persists for at least one week after infarction.

Isolated RVI is extremely rare. A patient with such (also with cor pulmonale and RV enlargement) demonstrated striking ST segment elevation in anterior and inferior leads mimicking acute anterior and inferior MI, and inferior Q waves.

Sinoatrial node dysfunction occurred in over one-half of cases of AIMI. Almost all cases of Sick Sinus Syndrome in infarction, have inferior MI.

Alterations in the P-R segment level and escape junctional rhythm occur in atrial infarction. Hemopericardium has caused tall peaked T waves and slow junctional rhythm and bradycardia (tamponade).

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MEDICAL ASPECTS OF NUTRITION

A Status Report on Diet, Nutrition and Cancer*

T. Colin Campbell, Ph.D.**

Current Positions on Cancer

Although investigations of a link between diet, nutrition and cancer can be traced back at least half a century, it is only within the last decade or two that a large number of such studies have been initiated in earnest. One of the first major conferences on this subject was held in 1975; since then, a large number of conference proceedings and reviews have been published.^{1, 2, 3}

A particularly influential review was that of Doll and Peto. These authors were commissioned by the Office of Technology Assessment of the U.S. Congress to evaluate the epidemiological evidence in support of a relationship of environment and cancer. They identified several types of environmental factors and concluded that on the basis of the literature they reviewed, diet could account for 10%-70% of cancer and, as a result, possibly be the most important environmental cause of human cancer. However, such a broad range in percentages indicated considerable uncertainty within the research community and/or the inability to accurately estimate the proportion of cancers caused by dietary practice. Other significant environmental causes included tobacco exposure (25%-40%), occupation (2%-8%) and alcohol (2%-4%).

Shortly following the completion of the review by Doll and Peto, the U.S. National Academy of Sciences (NAS) was contracted by the U.S. National Cancer Institute to conduct an in-depth review of the research literature on diet, nutrition and cancer. An expert scientific panel was convened in 1980 and included experts in diverse disciplines, such as biochemistry, microbiology, embryology, epidemiology, experimental oncology, internal medicine, microbial genetics, molecular biology, molecular biology, molecular genetics, nutrition, nutrition education, public health and toxicology.

These recommendations generally conform with the U.S. Dietary Guidelines for Americans which were previously published jointly by the U.S. Department of Agriculture and the U.S. Department of Health, Education and Welfare (now the Department of Health and Human Services).⁶ The earlier recommendations were largely based on studies showing a relationship between dietary practice and risk of cardiovascular diseases. Since the release of the NAS report on diet, nutrition and cancer, similar dietary guidelines have been or soon will be published by the American Institute for Cancer Research, the American Cancer Society and the U.S. National Cancer Institute (NCI).^{7, 8, 9}

Current Research Activities

Paralleling the explosive interest in this topic on the part of the public information agencies is a similar increase in research activity within the scientific community. The U.S. National Cancer Institute is now funding more than twenty human intervention trials to test the effectiveness of various nutrients in reducing cancer risk.¹⁰

In addition, there has been a sharp increase in the past five years in the number of investigator-initiated research projects now funded by NCI. The nutrients currently being studied by NCI include vitamins A, C and E and the trace mineral selenium. These intervention programs are organized so that appropriate population groups are enlisted and a careful analysis of the efficacy, dosage form and amount are undertaken before the study is begun.

It is too early to speculate on what type of data these studies will produce. One could speculate that, although a statistically significant positive effect may be produced, only a limited number of individuals particularly deficient in the study nutrient would respond. The implications of a negative result would also have to be evaluated with considerable caution since single nutrient effects may only comprise a small proportion of the total

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The first of its two reports was nearly 500 pages in length and summarized the panel's findings on the contributions of individual dietary constituents to cancer causation.⁵ Rather than trying to estimate a specific proportion of cancers caused by diet, the panel concluded that "cancers of most major sites are influenced by dietary patterns."

The panel believed that any estimates of specific proportions of cancer caused by dietary practice could be misleading. The fact that the disease is multifactorial suggests there would be great difficulty in determining how much the clinical onset of cancer might be delayed or prevented by dietary practice, as opposed to the manipulation of other exposure conditions. Furthermore, the extent to which dietary, as well as nondietary, risk factors would operate in different individuals could also be highly variable.

On the basis of the evidence reviewed, the panel also found that it was possible "to formulate interim dietary guidelines that are both consistent with good nutritional practices and likely to reduce the risk of cancer." Although priorities were not assigned to the six interim guidelines, the two that will likely have the most impact in the marketplace were the recommendations 1) to reduce dietary fat intake from the current 40%-45% to 30% of caloric intake and 2) to emphasize "the importance of including fruits, vegetables and whole grain cereal products in the daily diet."

dietary effect and, as a consequence, such negative results should not discredit the general dietary theory, which considers multiple factors.

A new nonprofit organization, the American Institute for Cancer Research, was recently organized for the purpose of funding research and public information projects on diet, nutrition and cancer interrelationships. The American Cancer Society has embarked on a major survey of putative relationships between lifestyle factors and cancer incidence.

Another program has been initiated at Cornell University, Ithaca, NY, to study the effect of multiple dietary risk factors in the causation of selected cancers in the People's Republic of China with major funding being provided by the U.S. National Cancer Institute, the China Center for Preventative Medicine and the U.S. Food and Drug Administration. This study includes 130 survey sites in China and will attempt to delineate not only the contributions to cancer risk of individual dietary components but also the significant interactions that may occur between such components. Previous nutrition literature would suggest that such interactions could be extremely numerous and substantial in their effects on cancer causation.

It is hoped by many that this activity and interest within the research and consumer communities will bring results within the coming decade that will enable the American public to make the appropriate modifications in their dietary practice to reduce cancer risk.

A Perspective to Evaluation of Literature

Most reviews catalog and evaluate mechanisms that might account for the effects of various dietary substituents. In spite of numerous hypotheses of mechanisms, it is unlikely that a common mechanism will be found for all substituents or even for individual substituents. Probably the more relevant question for this review is whether the evidence supporting a causative effect of dietary substituents or foods on cancer risk is strong enough to warrant the development of guidelines.

The strength of that evidence may be evaluated by examining the consistency of results within varios human studies, within diverse animal studies, and between human and animal studies. From that perspective, there is considerably more strength of evidence within this literature than is initially apparent. For example, let us consider only the relationship between dietary fat intake and colon cancer risk within various epidemiological studies (i.e., do not consider the vitamin A effect for sake of this example). Statistically significant results from such studies may exhibit either a positive relationship (as fat intake increases, cancer risk increases), an inverse relationship or no relationship. Those are the only three possibilities.

With this strategy, the multiple studies so far reported clearly show that as fat intake increase, colon cancer risk increases. Many of these studies show a positive relationship, some report no relationship and virtually none report a negative relationship. Furthermore, when that strategy is judged against a) the knowledge that epidemiological methodology is crude and will underestimate a real relationship and b) the knowledge that most of the studies reporting no relationship were undertaken in the more homogeneous population groups, the strength of the evidence between dietary fat intake and colon cancer risk becomes even more impressive.

A strategy of this type gives a new perspective to the evaluation of the nutrition and cancer literature. More consistency of data suddenly appears, as opposed to the inconsistency that would obviously exist if some studies were to show a positive relationship, some no relationship and some a negative relationship. When the literature is evaluated in this way for each nutrient, cancer risk increases with higher intake of dietary fat and protein and lower intakes of vitamin C, vitamin A (as beta carotene), vitamin E and dietary fiber. This conclusion does not imply that we should expect every study or every population group to exhibit these effects, only that when there is an effect, it will be highly probable that the direction of the effect will be as indicated.

The most significant implication of these data is that a compilation of these nutrient effects strongly suggests that a diet enriched in plant products reduces cancer risk. A diet emphasizing fruits, vegetables and whole grain products, as recommended by the NAS report, would provide the proper intake for each of these nutrients. This recommendation to increase the consumption of plant products is in accord with similar recommendations on diet and other chronic diseases, such as cardiovascular disease and diabetes. Future research should be addressed to the dissection of mechanisms as well as to a more definitive understanding of the relationship between cancer risk and various levels of nutrient intake.

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AFILIADO

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DIAGNOSTICO ANGIOCARDIOGRAFICO



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TQ es una niña de 6 meses de edad con un soplo cardíaco detectado a los 21 días de edad. Fue producto de un embarazo a término, con peso adecuado para su edad y sin complicaciones en el período neonatal. A la edad de 2 meses tuvo un episodio severo de bronquiolitis con bronconeumonia, durante el cual desarrolló insuficiencia cardíaca requiriendo digitalización. En el curso de los siguientes tres meses tuvo dos episodios adicionales de infecciones de las vías respiratorias, permaneciendo con un peso bajo la percentila 3 para su edad.

Al examen físico se apreciaba un infante sin cianosis, discretamente taquipneica, con una frecuencia cardíaca normal. Su presión arterial era 100/50 mm Hg, con un precordio dinámico e impulso apical palpable en el 5to. espacio intercostal izquierdo a nivel de la línea axilar anterior. Había frémito en el borde intercostal izquierdo superior y un soplo pansistólico, rudo, gr IV/6 en el segundo espacio intercostal izquierdo. Su acentuación era tarde en sistole, sobrepasaba el segundo sonido cardíaco y tenía irradiación amplia por el precordio y la espalda. Era posible detectar un soplo mesodiastólico, de baja tonalidad, en apex y el S₂ estaba acentuado. No había visceromegalia y los pulsos eran "saltones" en todas las extremidades.

El electrocardiograma demostraba hipertrofia ventricular izquierda y la radiografía de torax cardiomegalia con agrandamiento atrial izquierdo, segmento pulmonar prominente e hipervolemia pulmonar.

El angiograma de la niña se ilustra en la figura 1.

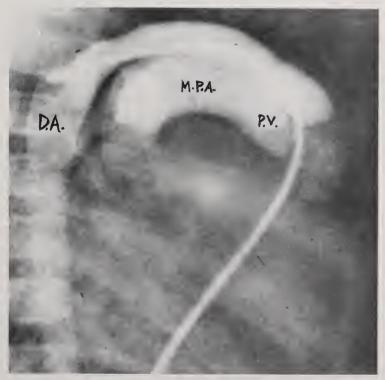


Figura 1. Angiocardiograma con el paciente en posición oblicua anterior izquierda. PV= válvula pulmonar, MPA= arteria pulmonar principal, DA= aorta descendente.

¿CUAL ES SU DIAGNOSTICO?

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Según Keith¹ el ducto arterioso patente (PDA) es la segunda cardiopatía congénita más frecuente. La incidencia verdadera de este defecto es difícil de determinar debido a las diferencias en la población con cardiopatías congénitas entre los diferentes centros y por la presencia del PDA en los neonatos pre-término, especialmente aquellos con problemas pulmonares. Se ha dicho sin embargo, que como defecto "aislado" el PDA constituye el 15% de las cardiopatías congénitas.²

El soplo que típicamente se describe en pacientes con PDA es uno continuo, de gran intensidad y timbre raspante en el precordio superior al margen izquierdo del esternón. No varía con la respiración ni posición del paciente y se propaga sobre el omóplato izquierdo. Sin embargo, en el infante con resistencia pulmonar elevada y en aquellos casos en que el cortocircuito de izquierda a derecha através del ducto es pequeño, el soplo es de carácter sistólico-eyectivo. En los pacientes con corto circuito de izquierda a derecha grande através del ducto hay usualmente un arrastre diastólico de baja tonalidad en el apex el cual también suele estar ausente en ductos pequeños y en aquellos con resistencia pulmonar elevada. La acentuación del S₂ y la presencia de un S₃ es también frecuente en los ductos arteriosos hemodinámicamente significativos. En los neonatos con trastornos respiratorios y persistencia del conducto arterioso el soplo es de alta tonalidad, "blowing" y sin componente diastólico. Si la resistencia vascular pulmonar alcanza el mismo nivel que la sistémica, el soplo puede desaparecer por

Hay escasa información sobre el porqué el conducto arterioso falla en cerrar en pacientes a término, sin otras cardiopatías y sin infección viral intrauterina. Se mencionan sin embargo factores hereditarios en la persistencia del conducto arterioso, ya que se ha descrito cierta tendencia familiar en la incidencia de este defecto congénito.³ Se reconoce también la mayor incidencia de PDA en el sexo femenino.

Los pacientes con PDA al igual que otros con corto circuito de izquierda a derecha están más propensos a desarrollar infecciones respiratorias repetidas como demostró nuestro caso. Los hallazgos electrocardiográficos y radiográficos en este caso son también los usuales en niños con PDA y cortocircuito de izquierda a derecha de magnitud moderada o severa. Aquellos con aumento significativo en la resistencia pulmonar vascular demuestran hipertrofia ventricular derecha en su electrocardiograma.

Basándose en un examen físico minucioso, principalmente en la auscultación del soplo, junto con el electrocardiograma, la radiografía de torax y el ecocardiograma, el diagnóstico clínico del PDA es casi siempre posible. Si estos pacientes requiren cateterismo cardíaco para la confirmación del diagnóstico es aún tema de discusión. En algunas instituciones, como el "Hospital for Sick Children" de Toronto, Canada, rara vez se hace cateterismo cardíaco en niños con los hallazgos clínicos y ecocardiográficos típicos de PDA. Ellos limitan este procedimiento invasivo a aquellos casos donde hay que determinar la resistencia pulmonar o excluir otros defectos asociados.

La persistencia del conducto arterioso puede demostrarse pasando el cateter desde la arteria pulmonar através del ducto hasta la aorta descendente. La anatomía del ducto patente puede demostrarse haciendo una inyección de material de contraste con el cateter colocado en la aorta descendente inmediatamente distal al extremo aórtico del conducto arterioso. La mejor posición para evaluar angiocardiográficamente el PDA es angulando el paciente a 60° en posición oblicua anterior izquierda. Hay ocasiones en que el ducto es pequeño o tortuoso y no se puede pasar a la aorta desde el lado derecho através de él. En ese caso debe hacerse un aortograma por vía retrograda de manera que se pueda delinear su anatomía satisfactoriamente.

El tratamiento quirúrgico del PDA aislado conlleva un riesgo mínimo en todos estos infantes por lo que la cirugía debe ser recomendada tan pronto se establece el diagnóstico. Se prefiere la división quirúrgica del ducto arterioso sobre la ligadura del mismo pues se siguen viendo casos de recanalización de ductos que han sido previamente ligados. La infusión de indometacina para el cierre farmacológico del conducto arterioso patente es solamente efectiva en los infantes pre-término durante los primeros días del período neonatal.

En los últimos años se han descrito nuevas técnicas para el cierre de los ductos arteriosos aislados mediante el uso de cateteres por vía femoral.⁵, ⁶ Estas técnicas han sido exitosas en casos seleccionados pero aun no se tiene suficiente experiencia en cuanto a sus resultados en infantes pequeños, neonatos y sobretodo en neonatos pre-término. Los propulsores de estas técnicas sienten optimismo en el sentido de que según se vaya aumentando su uso se adquiera la experiencia necesaria para justificar la aplicación de las mismas en la mayoría de los pacientes que requieran el cierre de su conducto arterioso patente.

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RESUMENES SEGUNDO CONGRESO PUERTORRIQUEÑO DE CARDIOLOGIA

01

EXPERIENCE WITH THE MEDTRONIC HALL VALVE. P. Altieri, E. Defendini, J. Martínez, H. Banchs, I. Lladó. Department of Medicine, Medical Science Campus, University of Puerto Rico.

In the last three years we have inserted 152 Medtronic-Hall Kaster valves, 78 were aortic (A) 73 mitral (M) and one tricuspid (T). Of the 78 (A), 45 were males and 23 females. In the (M) 23 were males and 50 females. In the (M) position the most frequent valve size was a #27 followed by #29, #31. In the (A) the most frequent valve size was #21 followed by #23, #25. 14 (P) had double valve replacement. 5 (P) with Marfan's Syndrome and aortic insufficiency had (A) replacement with a composite graft and reimplantation of the coronary arteries. The total mortality was 6% and all causes were not valve related. 3% had a late death due to congestive heart failure, 1.9% of sepsis and 4% of other causes including renal failure, bleeding and some surgical technical complications. No paravalvular leaks have been found. There have not been any valvular dysfunction, valvular thrombosis and only 2 episodes of transient embolic brain episodes. During surgery in the mitral position it is important to position the large orifice posteriorly and inferiorly because in this way we will avoid interference of the septum with the valve leaflet and to direct the flow to the apex and not to the free wall of the ventricle. All (P) have been anticoagulated.

In conclusion the Medtronic-Hall valve is an excellent valve hemodynamically, and in the minimal incidence of complications.

02

LEFT VENTRICULAR DYSFUNCTION DURING RIGHT VENTRICULAR PACING. P. Altieri, J. Martínez, H. Banchs. Department of Medicine, Medical Science Campus University of Puerto Rico.

The function of the right and left ventricle are interrelated by way of the concept of interdependence. It is known that right ventricular pacing will produce right ventricular dysfunction. The importance of this is seen when the left ventricular function of twenty patients (P) was studied by echocardiography and arterial blood pressure during right ventricular and A-V sequential pacing. Six (P) below 60 years showed a systolic blood pressure reduction of 11 mmHg and those (P) above 60 years showed a systolic blood pressure drop of 42 mmHg during right ventricular pacing, but not during A-V sequential pacing. There was a statistically significant reduction in the end-diastolic dimention of the left ventricle from 3.8 to $3.1 \, \text{cm} \, (P < .005)$ and in the ejection fraction from 46% to 41% (P < .005) when the A-V sequential pacing was changed to right ventricular pacing. In most of the patients the interventricular septum flattened or became paradoxic during ventricular pacing.

In conclusion right ventricular pacing, especially in the elderly will produce right ventricular dysfunction which will produce left ventricular dysfunction due to ventricular interdependence.

03

THE USE OF A-V SEQUENTIAL PACEMAKERS
IN THE MANAGEMENT OF PATIENT WITH
SINCOPE AND PROLONGED H-V INTERVAL.
H. Banchs, P. Altieri, J. Martínez, E. Defendini.
Department of Medicine, Medical Science Campus,
University of Puerto Rico.

Twelve patients (P) were referred to our institution due to syncope 5 (P) showed sinus bradycardia with a first degree A-V block, 4(P) CRBBB, 2(P) CRBBB (one with a first degree A-V block the other with a L.A.H.) and one an inferior myocardial plus a first degree A-V block. All underwent electrophysiologic studies including atrial and ventricular pacing. The A-H interval was normal with a mean value of 97 ± 22 msec. The sinus node recovery time was normal with a mean value of 1276 \pm 200 msec. The H-V was prolonged with a mean value of 85 ± 27 msec. No ventricular tachycardias were produced with ventricular pacing. Carotid sinus massage was done without any detected abnormalities. In all a Medtronic DDD 7000 A pacemaker was installed. The mean selected A-V interval of the pacemaker was 102 ± 97 msec. No arrhythmias has been detected postoperatively with serial Holter monitoring. The patients has remained asymptomatic.

In conclusion patients with syncope and prolonged H-V interval can be managed with A-V sequential pacemaker and in this way maintain a normal hemodynamic status.

04

INORGANIC PHOSPHATE IN ACUTE
MYOCARDIAL INFARCTION. H García, C Rosario,
JM Aranda, and E Hernández, Veterans Administration
Hospital and University of PR School of Medicine,
San Juan, Puerto Rico.

Previous studies have suggested that the level of serum inorganic phosphate (SIP) falls in patients (pts) with acute myocardial infarction (AMI). In order to define its clinical significance we began a prospective study of all pts admitte to the CCU of the San Juan VA Hospital during a 4 month period. Pts qualified if they had had chest pain within 24 hours of admission, had a serum creatinine of 1.5 mg% or less and had at least one SIP determination during hospitalization. Pts were classified according to the presence (34 pts) or absence (58 pts) of an AMI. The mean ± S.D. SIP in mg/dl according to inhospital day is depicted below:

	AMI (N=34)	No AMI (N=58)
Day 1	3.6±.68	3.4±.88
Day 2	$3.6 \pm .59$	$3.5 \pm .72$
Day 3	$3.5 \pm .89$	$3.7 \pm .86$
Day 4	$3.6 \pm .98$	$3.6 \pm .73$
Day 5	3.4 ± 1.12	$3.7 \pm .44$

P>.05 for all values between both groups. Both groups were similar in regard to the prevalence of diabetes mellitus, hypertension, use of antiacids or alcohol abuse. Six pts (18%) of the AMI group and I0 pts (17%) of the non AMI group had hypophosphatemia (SIP < 2.5 mg/dl). The incidence of congestive heart failure (CHF) was significantly higher in the low SIP subgroup of the AMI pts (83% vs I4%, p.<01). We conclude that caution must be taken in using SIP as an indicator of AMI. However, in AMI pts, a low SIP correlates with the presence of clinical CHF.

05

LEFT VENTRICULAR THROMBOSIS IN ACUTE ANTERIOR MYOCARDIAL INFARCTION Pérez-Rivas JF, Hernández-López E, and Linares E. San Juan V.A. Hospital, San Juan, Puerto Rico.

Left ventricular thrombosis is (LVT) is a frequent complication of acute transmural myocardial infarction of the anterior wall (AMI) with an incidence of peripheral embolization (PE) of up to 86%. Two dimensional echocardiography (2DE) can accurately identify patients (pts) with LVT.

As part of an ongoing study, 2DE has been performed in pts with AMI admitted to the CCU of the San Juan V.A. Hospital since June, 1984. In a 6 months interval, of 20 pts admitted with AMI, 15 (75%) underwent 2DE and average of 4.5 days after admission. LVT was identified in 6 (40%; group A) pts and was absent in 9 (60%; group B) pts. The clinical characteristics of these pts are depicted in the following table:

	Group A (N=6)	Group B (N=9)	Р -
CHF	100%	11%	.003
Previous MI	50%	11%	NS
Arrhythmias	33%	22%	NS
Death	17%	0%	NS
PE	0	0	NS
Max. CPK	1915U	212OU	NS

MI=myocardial infarction

After a mean follow-up of 4.3 months no embolic events have been identified in any of the group A pts. Two pts in this group have died. In 3 of the 4 long term survivors of group A pts who have had follow-up studies, the 2DE findings of LVT have decreased considerably. Thus, in our experience: 1) the incidence of LVT in AMI is high and usually associated with CHF, 2) PE was not clinically present and 3) spontaneous resolution is frequent.

06

VALUE OF QRS SCORING SYSTEM IN ESTIMATING EJECTION FRACION Sandra C. Gracia, M.D., Associate, Kermell A. Ocasio, M.D., Associate, Félix M. Cortés, M.D., F.A.C.P. Damas Hospital, Ponce, Puerto Rico

The QRS Scoring system developed by Silvester and modified by Wagner has been subject of several paper to asses its correlation with the Ejection Fraction by radionuclide studies. This system was used in our Institution in an attempt to confirm the correlation between the calculated Ejection Fraction using this method and that obtained by radionuclide imaging, good correlation of the calculated Ejection Fraction by the two methods was present only in patient with Acute Anterior Myocardial Infarction.

The correlation coefficient between Ejection Fraction using the QRS Score and using the ventriculogram was 0.76 for all acute myocardial infarction. We could not find a good correlation in cases with inferior myocardial infarctions or cardiomyopathies.

At this state the radionuclide ventriculogram remains the best non invasive method of obtaining the actual Ejection Fraction, nevertheless, the left ventricular Ejection Fraction can be safety estimated just by looking at the electrocardiogram in the subset of patients with Acute Anterior Myocardial Infarction.

07

INFLUENCE OF THE SITE OF MYOCARDIAL INFARCTION ON THE ST SEGMENTS SHIFTS DURING EARLY EXERCISE TESTING AFTER AN ACUTE MYOCARDIAL INFARCTION Rosario CV, Pedrosa C and Linares E. Veterans Administration Hospital and University of Puerto Rico School of Medicine, San Juan, P.R.

The purpose of this study was to correlate the type of ST segment deviation provoked by treadmill testing early after myocardial infarction (MI) with the site of the MI. A

total of 114 patients (pts) were exercised an average of 21 (range 6 to 29) days after the MI. Of the 48 pts with anterior wall MI (AWMI), 20 (41.6%) had resting ST segment elevation (ST \(^+\)) while 14 of the 66 pts (21.2%) with inferior MI (IWMI) did. This difference was statistically significant (p<.05) ST \uparrow occurred in the same site as the infarct in 73% of all pts. Early exercise testing provoked new or additional ST \(\) in 11 of 48 pts with AWM1 (22.9%) compared to 3 of 66 pts with IWMI (4.5%), (p < .001). While associated with AWMI, exercise induced precordial ST \(\) was not related to ST depression (ST↓) in the inferior leads. Among 66 pts with 1WMI, exercise testing produced ST \$\psi\$ in 14 (21.2%) compared to 12 of 48 pts (25%) with AWMI (p=NS). Neither exertional ST \(\psi \) nor ST \(\psi \) correlated with one-year cardiac mortality, recurrent MI or unstable angina. We conclude that exertional ST \(\) occurs significantly more frequent in AWMI than in IWMI, and that ST \u22c4 occurs with the same frequently in both types of location.

08

EVALUACION DE PRAZOSIN EN P.R. COMO AGENTE DE PRIMER PASO Y MONOTERAPIA EN EL TRATAMIENTO. Pedro J. Colón Ortiz, M.D. Laboratorio Cardiovascular, Caguas, Puerto Rico.

Considerando los recientes conocimientos sobre los efectos metabólicos/hemodinámicos de las drogas antihipertensivas más usadas, el objetivo de este proyecto fue evaluar la eficacia de Prazosin como agente único (monoterapia) en el tratamiento inicial (primer paso) de pacientes con hipertensión leve y moderada.

Se establecieron unos criterios de selección, cualificando 215 pacientes. De los pacientes seleccionados se analizaron las fichas de 158 pacientes debido a que 57 fueron separados del programa por no cumplir con las instrucciones.

De los 158 pacientes que completaron el programa, 42.3% corresponden a hombres y 57.7% a mujeres. La edad promedio para los pacientes femeninos fue de 50 años y para los masculinos 48.

Cientodiecinueve (119) pacientes (75.32%) fueron hipertensos leves y 39 (24.68%) fueron moderados al inicio del tratamiento.

La enfermedades concomitantes más frecuentes fueron Diabetes Mellitus, Asma Bronquial y algún grado de insuficiencia Renal. Se reportó historial familiar de hipertensión en el 64% de los pacientes.

La evaluación de la eficacia de Prazosin se analizó en 3 fases: Fase I (F¹), Fase 2 (F²) y Fase 3 (F³) según los requerimientos de Prazosin.

Nuevos hipertensos fueron iniciados en I mg. de Prazosin b.i.d., por 15 días. Pacientes tomando otros agentes anti-hipertensivos pasaron por un período de "Wash-Out" antes de iniciar el tratamiento con Prazosin. Si no se controlaban su presión en esta dosis pasaban a la F²-2 mg. de Prazosin b.i.d. por 15 días y si persistían hipertensos se seguían en F³ por 15 días a razón de 2 mg. de Prazosin en Ia mañana y 4 mg. al acostarse.

Un total de 97.5% (154) de los pacientes fueron controlados dentro de las primeras tres fases. Ochentaiseis porciento (86%) de los pacientes (N=136) fueron controlados en Fase 1 con 1 mg. b.i.d. de Prazosin, 10.7% de los pacientes fueron controlados en Fase 2 con 2 mg. b.i.d. de Prazosin y un paciente (0.8%) fue controlado en Fase 3 con 2 mg. en la mañana y 4 mg. antes de acostarse.

El resto de los pacientes (N=4) (2.5%) no regresó para evaluación final de la F^3 .

Sólo 13 pacientes (9%) reportaron efectos secundarios, los cuales fueron transitorios y ninguno requirió descontinuar el tratamiento.

La evaluación demuestra que Prazosin es efectivo como terapia inicial de pacientes con hipertensión leve y moderada.

También se esbosa los últimos conocimientos en relación a la polémica sobre el uso de diuréticos y otras drogas antidrenérgicas y la importancia de individualizar el tratamiento de la hipertensión esencial, teniendo en cuenta la concomitancia de hipertensión con otras enfermedades crónicas comunes como Diabetes Mellitus y Asma Bronquial.

09

BLOOD PRESSURE RESPONSE DURING DYNAMIC EXERCISE AFTER LONG TERM THERAPY WITH VERAPAMIL IN ARTERIAL HYPERTENSION Rodríguez M, Aranda JM, Pedrosa C, Rosario C, Martínez-Barroso J, García H. University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

Cardiovascular morbidity in hypertensive patients is directly related to the height of the systolic and diastolic blood pressure. The correlation is closer if the effects of exertion on blood pressure are taken into account. At present the effect of treatment with verapamil on these pressor responses remains to be determined. The objective of this one year study was to investigate the effect of chronic verapamil therapy on blood pressure (BP) response during dynamic exercise. The study group consisted of 49 patients (pts) with a sitting diastolic blood pressure (SDBP) \geq 95 and \leq 114 mm Hg. The dose of Verapamil (V) required to maintain the SDBP < 90varied from 160 to 480 mg/day. Hydrochlorothiazide (HT) was given in doses of 12.5 to 100 mg/day if BP control was not achieved with V. The initial mean SDBP was 102±6 mm Hg. After 52 weeks of therapy, the mean SDBP was 83±5 mm Hg. Graded exercise tests (ET) were performed after 52 weeks of therapy in a subset of 9 pts who had SDBP < 85 mm Hg throughout the one year period (mean SDBP 80±0). There was a significant increase in diastolic pressure recorded at the peak of the dynamic ET (mean 106 ± 6 , p < .01). A sustained therapeutic effect of V is present after one year of therapy. Its action appears to be potentiated by the administration of HT. A hypertensive response during dynamic exercise is observed after long term therapy.

10

STRESS THALLIUM-201 IMAGING IN PATIENTS WITH ARTERIAL HYPERTENSION, CHEST PAIN AND NORMAL CORONARY ARTERIOGRAPHY. H. García, MD, R. Bordewyk, MD, J. Martínez, MD, J. Rivera, MD, E. Hernández, MD, and J.M. Aranda, MD. Cardiology Section and Nuclear Medicine Service, VA Medical Center, San Juan, Puerto Rico.

Positive exercise thallium-201 scintigraphy (201-TL) has been reported in patients (PTS) with chest pain and normal coronary arteriography. The largest proportion of these "false positive" 201-TL has been in PTS with hypertrophic (not hypertensive) cardiomyopathy. To our knowledge, no study has specifically addressed this issue in PTS with arterial hypertension and normal coronary arteriography. We undertook this study to elucidate the validity of exercise 201-TL in hypertensive PTS with or without left ventricular hypertrophy (LVH), chest pain and normal coronary arteriography. All coronary catherization reports done from June 1983 to December 1984 were reviewed for the identification of PTS with nonsignificant obstructive coronary disease and chest pain. Those PTS who were hypertensive as defined by the American Heart Association criteria and had LVH determined by echocardiogram (echo) and/or EKG were called group A. If LVH was absent, they were included in group B. A third group of young asymptomatic normotensive volunteers with normal echo was the group C. An exercise 201-TL test was done in all and interpreted blindly.

_	No. of PTS	Mean Age	Abnormal 201-TL
Group A (LVH)	11	52.4	9 (82%)
Group B (NO LVH)	4	55.7	3 (75%)
Group C ("Normals")	6	27.1	0

These findings suggest that exercise 201-TL is an inadequate screening study for obstructive coronary disease in hypertensive PTS with chest pain. The cause of these perfusion defects remains to be determined.

11

DESARROLLO, MODO, SEGUIMIENTO Y TRATAMIENTO DE LA PACIENTE CARDIACA DURANTE SU EMBARAZO Y PARTO. Experiencia durante 14 años en la Clínica de Cardiología Obstétrica. Francisco Veray, MD, José Hawayek, MD.

Durante catorce años consecutivos en la Clínica de Cardio/OB en el Proyecto Materno Infantil (MIC) en el Centro Médico de Puerto Rico, hemos visto la gama de problemas cardiológicos en la paciente embarazada.

Estas experiencias obtenidas nos han ayudado a desarrollar una modalidad de seguimiento y tratamiento para estas pacientes complicadas. En este tiempo se evaluaron 63,000 pacientes embarazadas, haciendo un total de 364,000 visitas prenatales. De éstas, alrededor de 5,000 son de la Clínica de OB/Cardio. La distribución de los problemas enfrentados se conforma a lo publicado de otras fuentes, siendo la mayoría soplos funcionales seguidos de enfermedad reumática cardiaca.

Se establecieron reglas para el manejo en la clínica, criterios para hospitalización y seguimiento en el hospital, así como el manejo del parto y puerperio. Con estas reglas logramos un mejor entendimiento por nuestros médicos y personal paramédico de la gama de problemas cardíacos y se tradujo en resultados sumamente favorables para nuestras pacientes.

En fin, creemos que esta modalidad de manejo del paciente obstétrico con problema cardiovascular es altamente viable para nuestro ambiente. Se enfoca desde una visión multidisciplinaria y ésto hace que mejore la excelencia de los resultados, mejorando así el prognóstico de nuestras pacientes.

12

A RARE RIGHT ATRIAL TUMOR SIMULATING CYANOTIC HEART DISEASE IN A NEWBORN Juan Villafañe, MD, Arthur Pickoff, MD, Gerard Kaiser, MD, Marcia Saltz, MD, Sharon Thompson, MD, Henry Gelband, MD. Jackson Memorial Hospital, University of Miami

This 36 hours old term infant developed cyanosis and tachypnea 12 hours prior to admission. Physical exam was compatible with Tricuspid Atresia. The ECG revealed RAE and LAD. The pulmonary blood flow on X-ray was diminished. Echocardiography revealed a large right atrial mass obliterating the tricuspid valve orifice. Cardiac cath and angio confirmed the presence of a large space occupying lession in the right atrium with secondary right to left shunting at atrial level. Because of significant desaturation, prostaglandin E was insituted with subsequent improvement of oxygen saturations and disapperance of metabolic acidosis. Surgical excision of a 2.3 x 2.0 x 1.0 cms rubbery, tan, right atrial tumor was performed the following day. Histologic examination revealed characteristic features of the intravascular variant of nodular fascitis. The post op course was satisfactory except for a brief episode of supraventricular tachycardia and a right pleural effusion. Subsequent ultrasound studies showed the right atrium free of extra echoes. Clinical evaluation to date revealed the infant to be asymptomatic. In summary, this newborn presented with a rare cardiac tumor in an unusual location, imitating "cyanotic congenital heart disease". Ultrasound studies were diagnostic. Prostagladin proved to be of benefit in this patient. To our knowledge this cardiac tumor has never been described in a newborn.

13

ECOCARDIOGRAFIA EN ENFERMEDAD DE KAWASAKI

Dres. Jorge Sánchez y José T. Medina CT Radiology Complex, Bayamón, Puerto Rico.

Sesenta pacientes con edades de 4 meses a 14 años, 31 varones y 29 niñas con diagnóstico clínico de Kawasaki se estudiaron después del período febril de la enfermedad con ecocardiograma de modo M y bidimensional en los últimos 30 meses. En 35% los trazados fueron seriados. Los trazados incluyeron la visualización de las arterias coronarias con eco bidimensional.

Un 70% demostró ecocardiogramas anormales, que fueron en orden de frecuencia: agrandamiento de atrio izquierdo, efusión pericárdica, movimiento disminuido del septo, en ninguno se visualizó aneurismas coronarios. La mayor parte de los trazados se normalizaron en aquellos con ecocardiogramas repetidos.

Este reporte indica que el ecocardiograma brinda suficiente información sobre las complicaciones cardíacas en pacientes con la enfermedad de Kawasaki; la ausencia de aneurismas coronarios en este estudio sugiere que la enfermedad puede ser más benigna en nuestro medio.

14

A DECADE OF PUERTO RICAN CONNECTION S. Subramanian, M.D., F.R.C.S., F.A.C.S., Professor of Surgery, State University of New York at Buffalo, Chief, Division of Cardiovascular Surgery, Children's Hospital of Buffalo

Between 1974 and 1984, a total of 308 patients came from Puerto Rico to Children's Hospital of Buffalo for the surgical treatment of congenital heart disease. Their ages ranged between 2 days and 29 years, mean age (4.4 years). Forty patients were 6 months of age or lower and 75 were less than one year old. One hundred seventy three (173) male 135 female patients. A wide variety of defects were treated. Common defects being: tetralogy of Fallot (59), VSD (41), TGA (29), ASD (27), pulmonary valve stenosis (27), pulmonary atresia (15) aortic valve stenosis (14), A-V canal (12) and double outlet right ventricle (8). Thirty-five children were admitted for emergency operations. Forty-four operations were palliative, which included shunts and banding. The remainder were reconstructive procedures. Forty-three patients underwent intracardiac surgery using profound hypothermia and circulatory arrest. In 14 small infants before 1976, ice packs were used for surface cooling. More recently, hypothermic chamber has been used. Out of the total of 308 patients, 293 (95%) survived the operation and left the hospital in good clinical condition.



TRANSLUMINAL BALLON COARCTATION ANGIOPLASTY: EXPERIENCE WITH 27 PATIENTS. Lababidi ZA, Daskalopoulos DA and Stoeckle H Am J Cardiol 1984; 54:1288-1291

Los autores, de la División de Cardiología Pediátrica del Hospital de la Universidad de Missouri reportan su experiencia de dos años donde realizaron la angioplastía de balón en 27 pacientes consecutivos con coartación de aorta (COA). Se incluyen en este número 7 infantes con COA preductal, 7 pacientes con recoartación y 13 pacientes con COA inoperada. Las edades fluctuaron desde 4 días a 27 años.

Los resultados fueron satisfactorios en todos los casos basándose en la reducción significativa del gradiente sistólico a través de la coartación y el aumento notable del diámetro de la coartación luego de la angioplastía de balón. La data indica que la angioplastía de balón para COA es un método seguro siempre y cuando se preste atención rigurosa a ciertos aspectos técnicos. La angioplastía de balón rasga la íntima arterial por lo que la posibilidad de ruptura de la aorta es una realidad. En el seguimiento de 24 meses luego de la angioplastía los autores no encontraron evidencia de formación de aneurismas.

Los autores opinan que la angioplastía de balón puede ser un procedimiento paliativo efectivo en los infantes seriamente enfermos con COA como parte del "síndrome de coartación" y luego efectuar la reparación quirúrgica cuando el riesgo sea menor. En los casos de recoartación y de COA inoperada, la experiencia con la angioplastía de balón ha sido muy buena. Sin embargo, para poder considerar este procedimiento como el definitivo en estos casos se necesita un seguimiento por un período de tiempo mayor del que se tiene hasta el presente

Rafael Villavicencio, MD, FACC

USE OF BALLON ANGIOPLASTY TO TREAT PERIPHERAL PULMONARY STENOSIS.
Rocchini AP, Kveselis D, Dick M, et al.
Am J Cardiol 1984; 54:1069-1073

La estenosis pulmonar periférica puede ocurrir como un defecto aislado, asociado a tetralogía de Fallot o como consecuencia de una anastomosis aortopulmonar. La reconstrucción quirúrgica de la arteria pulmonar hipoplásica o estenótica es díficil y muchas veces imposible. La sección de Cardiología Pediátrica del Hospital de Niños C.S. Mott de la Universidad de Michigan, informa sus resultados en la angioplastía de balón en 13 pacientes con estenosis pulmonar periférica.

Los criterios para considerar una angioplastía exitosa fueron: aumento de 75% en el tamaño de la arteria pulmonar con relación a sus dimensiones antes del procedimiento, reducción del gradiente sistólico a través de la estenosis en un 50% ó un aumento en el flujo pulmonar mayor de 25%.

De 13 niños estudiados, 5 tuvieron angioplastías exitosas con un seguimiento de 6 a 30 meses. En 8 pacientes la angioplastía no tuvo éxito, cuatro de ellos eran estenosis en el lugar de anastomosis aortopulmonares previas y los otros 4 por dificultades técnicas. En un caso hubo perforación de la arteria pulmonar derecha. El fallo en lograr dilatación arterial en los casos de anastomosis quirúrgica previa se cree es porque la estrechez en ellos ha sido causada por un proceso de fibrosis externa y no por un defecto de la pared arterial.

Aunque la angioplastía de balón no fue efectiva en todos los casos, sí proveyó mejoría significativa en ciertos pacientes donde el manejo quirúrgico por lo regular no tiene éxito.

Rafael Villavicencio, MD, FACC

CARACTERISTICAS DE MENINGITIS EN EL ENVEJECIENTE. Gorse GJ, et al. Arch Int Med 1984; 144:1603

Según los individuos envejecen, estos se convierten en más susceptible a las formas serias de meningitis. La población geriátrica aparentemente, tiene tejido neurológico el cual es más fácilmente atacado por patógenos bacterianos y se ha demostrado un aumento en la morbilidad y mortalidad. Gorse y su colaboradores condujeron un estudio retrospectivo de 71 pacientes con edades de igual o mayor de 50 años y 138 entre las edades de 15 a 45 años con el diagnóstico de meningitis para identificar características única en el paciente envejeciente. En el grupo de edad más avanzada, 54 (76%) tenían meningitis

bacteriana, 9 (13%) tenían meningitis granulomatosa, y 9 (11%) tenían meningitis aséptica. En el grupo de edad más joven el 32 (23%) tenían meningitis bacteriana y 97 (70%) tenían meningitis aséptica. Entre los casos de meningitis bacteriana en el grupo de más edad, Streptococcus pneunomiae fue responsable de 13 (24%) y los bacilos entéricos gram negativos por 9 (17%). Complicaciones serias ocurrieron en 38 (70%) de los pacientes envejecientes con meningitis ocurrió en 24 (44%) de los pacientes envejecientes comparado con 4 (13%) de los pacientes más jóvenes. En ambos grupos los signos y síntomas de meningitis fueron fiebre, naúsea, vómito, rigidez de nuca, dolor de cabeza y confusión. A pesar de que en los pacientes envejecientes con meningitis neumococcica tenían unas tasas más alta de confusión. Los pacientes envejecientes con meningitis bacteriana tenían más frecuentemente uno o más de las enfermedades subvacentes o que predisponen a esta condición y la condición de su estado mental al momento del diagnóstico eran más severas. Los procedimientos neuroquirúrgicos en ambos grupos aparentemente están asociados con una incidencia más alta de meningitis por bacilos gram-negativos.

Comentarios: Hay un grupo de funciones que se deterioran con la edad que predisponen a meningitis. La integridad del sistema vascular y del sistema nervioso disminuyen haciendo a este sistema nervioso central un lugar en donde es más fácil que ocurra infección; la actividad de anticuerpos del hospedero disminuye, la habilidad de ésta para combatir meningitis una vez establecida; disminuye la quemoluminiscencia de las células blancas (que es un marcador de la efectividad de estas células en matar bacterias) disminuye; y otros cambios en otros sistemas de órganos. Desde aumento en el volumen residual de la vejiga urinaria hasta una disminución en la depuración bacteriana de los pulmones establecen el ambiente propio para que ocurra invasión de las bacterias a la sangre y posiblemente ocurra sembrado en las meninge por estas bacterias. Este estudio claramente apunta a una morbilidad y mortalidad aumentada y describe en una forma precisa la frecuencia aumentada de meningitis séptica vs aséptica en la población de envejecientes. Por estos hallazgos el médico debe estar alerta a cualquier cambio en el estado mental del envejeciente o en el desarrollo de focos neurológicos localizantes. El paciente envejeciente puede que no presente fiebre y muchas veces solamente está levemente confundido de tal manera que las destrezas clínicas en la evaluación del paciente y en reconocer aún cambios sutiles es mandatoria para un rápido diagnóstico de meningitis.

C. Ramírez-Ronda, MD, FACP

INJECTION THERAPY FOR HERNIATED DISCS, BACKGROUND AND USEFULNESS. Fisher RG Post-Graduate Medicine 1984; 75(8)

Sciatica and low back pain occurs in 50% of adults at some time of their lives, resulting in temporary disability. The most common cause is a prolapsed intervertebral

disc. Correct diagnosis is still the critical step to the success of therapy. Signs and symptoms include motor (paralysis or paresis), sensory (numbness, paresthesias), and vasomotor deficits (claudication; changes in skin color and temperature). The diagnosis is to be supported which is presently having excellent results. In 75% of cases be treated conservatively with success, involving bed rest, heat, diathermy, corset, traction, exercises, analgesics and muscle relaxants. However, in 30% of patients, this treatment fails and surgery involving laminectomy or diskectomy is needed. There is a new alternative to surgery, intradiscal nucleolysis or chemonucleolysis. which is presently having excellent results in 75% of cases used, results equal or better than surgery itself. It consists of an intradiscal injection of a chondrolytic enzyme, such as chymopapain or collagenase, resulting in dissolution of nucleus pulposus matrix which causes a relief in pressure of the herniated material on nerve endings. Chymopapain is a derivative of papaya latex, used as a meat tenderizer and skin debridor in burns. Its most serious complication is hypersensitivity reaction, with a 1% incidence, and few cases of fatal anaphylaxis. Pretreatment with anti-histamines or steroids and close monitor of vital signs have reduced risks. However, collagenase, isolated from Clostridium histolyticum and recently approved by the FDA, shows promising success because unlike chymopapain, no hypersentivity reactions have occurred, and does not cause demyelinization or disturbance of microvasculature in peripheral nerve fibers. Intra discal nucleolisis will also decrease length of hospital stay and cost as compared to surgery. However, it will never replace laminectomy in cases where rapid neurological deficits are occurring, such as in cauda equina syndrome.

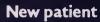
Anna V. Cintrón, MD

LEG ULCERS. Lofgren E Postgraduate Medicine 1984; 76:51-54

Circulatory problems are often insidious, an ulcer on a lower extremity may be the first clue and is almost always due to an underlying disorder that must be recognized and controlled if progression or recurrence is to be prevented. Venous insufficiency is by far (90%) the most common cause, with arterial insufficiency being the second most frequent (8%) and other diseases, like bacterial, mycotic, neoplastic, neurological and systemic disorders, besides trauma, accomplish the other 2%. Venous ulcers are best treated with topical medication such as an aqueous solution of aluminum subacetate 0.25%, elastic support and leg elevation, being effective over ninety percent of the time. Biopsy and culture are required if the ulcer is of unknown cause or does not respond promptly to treatment.

José R. Busquets, MD

What can you do for hypertensives like Don S?



Workup at 56 shows a systolic of 162 mmHg, diastolic of 100 mmHg.

Dislikes taking medication

Prior to last year, never sick in his life. Hates the thought of yet another medication.

Loves foodBut often eats on

the run...vows to be more careful.

Coexistent ulcer

Previous physician put him on cimetidine.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

STR-

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy
Don S represents 899 black patients between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.1

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even in Don S's racial and age

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Compatible with cimetidine and ranitidine

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when administered concomitantly with cimetidine or ranitidine. This compatibility of TENORMIN with today's widely prescribed H₂ receptor antagonists makes it a logical choice for hypertensives like Don S who are under treatment for a coexistent ulcer.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁶ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.1



For Don S...and virtually all your hypertensive patients

ONE TABLET A DAY TENORMIN (atenolol)



ONE TABLET A DAY TENORM (atenolol)



TENORMIN* (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[1-methylethyl) amino] propoxy]. Atenolol (free base) has a molecular weight of 266 ft is a relatively polar hydrophilic compound with a wafer solubility of 26.5 mg /ml at 37. C and a log partificing coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg. ml at 25. C) and less soluble in chloroform (3 mg. ml at 25. C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type duirefue.

Iniazide-fype diuretic

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and attenoid slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and for be given a diuretic and the response observed closely. It cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases,

in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overtangina pectoris, when disconfinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

drawal symptoms occur
Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta;-stimulating agent (bronchodilator) made available. If dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery in this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask fachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with
impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholarmine-depleting drugs (eg., reseptine) may have an additive effect
when given with beta-blocking agents Patients treated with TENORMIN plus a catecholarmine
depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine
concurrently, the beta blocker should be discontinued several days before the gradual withdrawal
of clonding.

of clonidine

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg kg 'day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg / kg / day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-

lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15~mg/kg/day or 7.5~times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300~mg but nof 150~mg atenolol $\,kg/day$ (150~and 75~times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo / fetal resorptions in rats at doses equal to or greater than 50 mg / kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg. kg or 12 5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human guilk. Since

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

Pediatric Use: Satety and effectiveness in children have not been established

Pediatric Use: Sately and ethectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transienf Frequency estimates were derived from confrolled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or ellicited (eg., by checklist—foreign studies). The reported frequency of ei-cited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo

Inless reactions were volunteered white address of the state of the st

teered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).
CENTRAL NERVOUS SYSTEM: NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), freaming (0%-0%).
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTAL SILL SAND FOREIGN STUDIES:

RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%) TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%) CENTRAL NERVOUS SYSTEM: NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), lighf-headedness (3%-0.7%), tiredness (26%-13%), latique (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%) GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%) RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%) MISCELLANEOUS There have been reports of skin rashes and for dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

tored tollowing cessation of interapy

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolo)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress Central Nervous System: Reversible mental depression progressing to catationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of firme and place, short-term memory loss, emotional liability with slightly clouded sensorium, decreased performance on neuropsychometrics
Gastrointestinal: Mesentienic arterial thrombosis, ischemic colitis
Other: Reversible alopecia. Peyronie's disease, erythematous rash, Raynaud's phenomenon.
Miscellaneous: The oculomicocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency freatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension,

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Amnophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one table it day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml. min. 1.73 m² (normal range is 100-150 ml. min. 1.73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml. min. 1.73 m²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage	
15-35	16-27	50 mg daily	
~ 15	>27	50 mg every other day	

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolot) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on into other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolot), round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Profect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on file, Stuart Pharmaceuticals **2.** Herman RL, Lamdin E, Fischetti JL, Ko HK Postmarketing evaluation of atenolol (Tenormin*). A new cardioselective beta-blocker *Curr Ther Res* 1983, 33(1) 165-171 **3.** Feely J, Wilkinson GR, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine N Engl J Med 1981, 304 692-695 **4.** Kirch W, et al. Influence of β-receptor antagonists on pharmacokinetics of cimetidine *Drugs* 1983. 25(suppl 2) 127-130 **5.** Spahn H, et al. Influence of rantidine on plasma metoproloi and atenolol concentrations Br Med J 1983, 286 1546-1547 **6.** Zacharias FJ Comparison of the side effects of different beta blockers in the treatment of hypertension. *Primary Cardiol* 1980, 6(suppl 1) 86-89



Medicolegal Decisions



NATUROPATH CONVICTED OF INVOLUNTARY MANSLAUGHTER

Evidence supported a naturopath's conviction of involuntary manslaughter based on testimony expressed as "reasonable medical certainty" rather than "beyond a reasonable doubt," an Idaho appellate court ruled.

An 86-year-old patient consulted a naturopath. He was given a "colonic irrigation" to relieve his severe constipation. He became weak during the treatment and had to be carried to his car when he left the office. The naturopath prescribed and dispensed digitalis for an apparent heart condition but did not suggest that the patient enter a hospital. The patient's relatives were told that he was well enough to make the trip home to Oregon. The next morning, he was admitted to a hospital in his home town, where he died the next evening.

The naturopath was charged with practicing medicine with out a license and causing the patient's death. At the trial, the physician who performed an autopsy on the deceased patient testified that he died as a result of acute heart failure and pulmonary edema. He and a second physician testified that the distension of the colon by means of an enema could aggravate or worsen heart failure. In answer to a hypothetical question, the second physician testified that in his opinion, to a reasonable medical certainty, in light of the fact that the patient's complexion was described as not unusual when he arrived and in a bluish condition when he left the naturopath's office there was a cause and effect related to the enema and his worsened condition. The naturopath was convicted of involuntary manslaughter.

On appeal, the appellate court said that the second physician established, to a reasonable medical certainty, a causal relationship between the enema and the deterioration of the patient's condition. The court said that the jury justifiably inferred that the patient's worsened condition led to his death, based on the facts that he had to be hospitalized the morning after the treatment and died soon thereafter.

The court said that it was not required to reverse simply because the physician's testimony was given in terms of reasonable medical certainty rather than beyond a reasonable doubt. Concluding that the evidence supported a permissible inference of causation by the jury, the court affirmed the judgment of conviction.—

State of Idaho v. Maxfield, 677 P.2d 519 (Ida.Ct. of App., Feb. 29, 1984)

BOARD SUSPENDS PHYSICIAN'S LICENSE FOR IMPROPERLY PRESCRIBING STEROIDS

A decision by the Board of Medical Examiners to suspend a physician's license for five years for improperly prescribing steroids was properly affirmed, a Hawaii appellate court ruled.

The physician treated three minor children with 5 mg, of prednisolone daily for allergic rhinitis. When they contracted chicken pox in June 1976, he ordered the prednisolone stopped. They became ill and were admitted to a hospital. Three other physicians examined them and concurred that all three were suffering from steroid complications.

A hospital peer review committee informed the physician that it intended to suspend his privileges for the inappropriate use of prednisolone. That decision was filed with the Board of Medical Examiners. On December 14, 1977, the board decided to proceed with a disciplinary hearing and requested the State Attorney General to initiate the proceeding. He did so in August 1980. A hearing officer was appointed, and he recommended suspension for not less than a year. The board adopted the hearing officer's findings, but ordered the physician's licence suspended for five years. A trial court affirmed the board's decision.

On appeal, the trial court's decision was affirmed. Admission of testimony by two physicians was not erroneous, the court held. They had obtained from the children's parents the medication they were administering, and the hospital pharmacy identified it as prednisolone. They testified that using steroids to treat allergic rhinitis was improper and that the administration of steroids to young children should be avoided.

The physician failed to show any prejudice from the four-year delay between the Board's receipt of notification of the peer review committee's adverse decision and the state's initiation of the disciplinary proceeding.—

Chock v. Bitterman, 678 P.2d 576 (Hawaii Intermediate Ct. of App. March 1, 1984)

COURT AUTHORIZES REMOVAL OF SUPPORT SYSTEM FOR INFANT

The interests of a terminally ill infant outweighed those of the state in preserving life by means of a life-support system, a Florida appellate court ruled.

The parents and legal guardians of a 10-month-old infant petitioned for approval to terminate the use of his life-support system. The infant was the second of twins, the first of whom was stillborn.

When he was born, the infant was asphyxiated, with very little spontaneous activity. He was in a chronic permanent vegetative coma, with more than 90 per cent of his brain function gone, without cognitive brain function, and terminally ill. He had no independent respiratory function and would die in a matter of hours if the ventilator was removed. It was estimated that with use of the ventilator he would probably not live beyond two years. The costs of his care were and would continue to be fully covered by insurance. The court authorized the parents to have the life-support system terminated and to instruct physicians to keep the infant comfortable and provide him with nutrition but not furnish life-sustaining procedures.

The state appealed, contending that its interest in preserving life outweighed the parents' assertion of the child's right of privacy to remove the life-support system. The state challenged the trial court's finding that the infant was terminally ill.

The court said that the record fully supported the trial court's findings that the infant's life was being sustained only through the use of extraordinary life-prolonging measures. A neonatologist pointed to a CAT scan and sonograms that confirmed his diagnosis of marked hypoxic ischemic encephalopathy with overwhelming destruction of brain tissue. He said that the condition was incurable and irreversible, characterizing the life-support system as merely postponing the child's death. Another neonatologist and a child neurologist concurred in the diagnosis and prognosis. The neurologist said that medically speaking, the infant had no life. The appellate court found that the proceedings in the lower court had been thorough and handled with great care and concern. Finding clear and convincing evidence to support the trial court's findings, the appellate court affirmed.—In re Guardianship of Barry, 445 So. 2d 365 (Fla.Dist.Ct. of App., Jan. 27, 1984)

FATHER OF MENTAL PATIENT WHO MURDERED FAMILY MEMBERS AWARDED \$92,300

Three physicians were negligent in discharging a state mental hospital patient who later killed his mother and brother, a federal appellate court for Kansas ruled.

The 19-year-old patient was found mentally ill by a probate judge on January 7, 1974, and ordered to enter a state hospital. He had threatened to kill his grandparents with a hatchet and meat fork. On April 19, 1974, a team

of physicians at the hospital decided that the patient was not dangerous to himself or others and discharged him. A week later he murdered his mother and brother.

His father filed a wrongful death action on behalf of himself and his other two sons against the physicians who participated in the discharge decision. A psychologist settled the claim against him before trial. A jury found in favor of the father for \$92,300.

On appeal, the federal appellate court certified two questions of Kansas law to the Kansas Supreme Court. The Supreme Court ruled that a claim arising out of a negligent release of a patient who has violent propensities is a valid cause of action. The court also said that staff physicians of a state mental institution are not immune from civil liability for release of a dangerous patient.

Deciding a few remaining issues, the appellate court said that the trial court did not abuse its discretion in allowing a psychologist to testify on the standard of care of the physician-defendants. The court said that the decision in question in volved psychological rather than medical inquiry and the expert was competent to testify. The court properly excluded testimony by the patient and a minister about the volatile and abusive family history. The court said the patient's theory of contributory negligence by the family in causing the deaths was invalid.

The trial court did not err in admitting a videotape of the patient made during his confession to the police on the day of the murders. The tape did not show the patient as a raving incompetent and was not unduly prejudical, the court said. The decision in favor of the father was affirmed.— *Durflinger v. Artiles*, 727 F.2d 888 (C.A.10, Kan., Jan. 27, 1984)

PATIENT SUES PHYSICIAN FOR DRUG ADDICTION

A patient who claimed he became addicted to drugs prescribed by his physician had a cause of action against him, an Oklahoma appellate court ruled.

The patient consulted the physician, an osteopath, for insomnia secondary to neck and back pain. He sold the patient about 1,125 units of Placidyl, Valium, Tuinal, and Tenuate, all controlled drugs, over the next 13 months. The patient claimed that as a result he had a severe addiction accompanied by an irresistible compulsion to commit crimes to finance his craving for drugs.

By the time he field suit against the physician for malpractice, he had been arrested seven times, had lost tow jobs, had four car accidents and three motorcycle accidents, had been divorced, had lost custody of his child, and faced a prision term of more than 20 years. He sought \$1 millon compensatory and \$1 millon in punitive damages. A trial court dismissed the complaint and the patient appealed.

Reversing the decision, the appellate court said the patient stated a claim for medical malpractice. Punitive damages could be recovered if the patient could show oppression, fraud, or gross negligence, the court said.—*McCarroll v. Reed*, 679 P.2d 851 (Okla.Ct. of App., Dec. 20, 1983; rehearing denied, Jan. 19, 1984; cert. dismissed, Okla.Sup.Ct., March 13, 1984)





AMERICAN ACADEMY OF PEDIATRICS

DON'T OVERLOOK A TEENAGER'S PAIN: IT MAY BE ASSOCIATED WITH STRESS

A teenager complains of a stomach ache, chest pain or a headache, yet no medical problem can be diagnosed. What can the pain the attributed to?

Stress, says a Vanderbilt University study, published in the January issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP). Researchers from that institution's Division of Adolescent Medicine report that recurrent abdominal and chest pain in adolescents could be related to negative stressful events in their lives.

Interestingly, the stressful event that affected a study of 172 adolescents most was failing grades on a report card (33.9 percent). That was followed by increased arguments between (not with) parents (28.3 percent), serious family illness (27.9 percent), breaking up with a boyfriend or girlfriend (27.8 percent) and death in the family (23.6 percent). Surprisingly, a parents' divorce ranked fifteenth on a scale of the top 20 stressful events in a teen's life (13.9 percent).

The sampling of adolescents, aged 11-19, were those who visited Vanderbilt's outpatient adolescent clinic during a six-month period. They filled out questionnaires that asked what stressful events they had recently experienced, if their perception of the event was good or bad, and how much impact the event had on their lives.

Patients with the recurrent stomach and chest pain for which no medical diagnosis was made had significantly higher negative life stress scores than patients seen for routine checkups or minor illnesses. Furthermore, patients referred for behavioral problems had the highest negative life stress scores.

This questionnaire was tailored directly to adolescents, listing stresses common to their age group. Although the majority of subjects in the study (67 percent) were female, the researchers indicate that there were no significant differences between the sexes.

The researchers maintain that although a causal relatioship cannot be assumed between pain and stress, this measurement can provide data for parents who are reluctant to consider stress as a possible factor in their

teeneger's symptoms. "It has been our experience that parents presented with this data more readily accept the potential role of stress ... (in complaints," they wrote.

WARNING SIGNS IN TEENAGE SUICIDES CAN BE DETECTED

Adolescent suicide has become a national concern, capturing the attention of television fiction as well as hard news reports. The media recently have reported the startling news that teen suicides sometimes occur in clusters— one suicide in a community often can stimulate a string of suicides among young people attending the same high school or group of schools.

You should know that suicidal tendencies are detectable. Studies show that teenagers who consider killing themselves give warning signs before their suicide attempts. The warning sings include many standard indications of depression:

- Noticceable change in eating and sleeping habits
- Withdrawal from friends and family
- Persistent boredom
- Decline in quality of school work
- Violent or rebellious behavior
- Running away
- Drug and alcohol abuse
- Unusual neglect of personal appearance
- Difficulty concentrating
- Radical personality change
- Psychosomatic complaints

A teenager who is planning to commit suicide might give verbal hints such as "I won't be a problem for you much longer," "Nothing matters," or "It's no use." The adolescent also might make "final arrangements" such as giving away favorite possessions or throwing away personal mementos.

Teenagers who commit suicide often feel that nobody needs them — that nobody cares. Many adolescent suicides occur shortly after a loss of some kind — the death of a friend, the breakup with a boyfriend or girlfriend, or parents' divorce.

Some estimates hold that adolescent suicide is the third leading cause of death among teenagers. Parents, brothers or sisters, friends and teachers who notice any signs that indicate the possibility of suicide should discuss them with the child or teenager. Don't be afraid that talking about suicide will cause the youngster to do it. Frank discussions about his or her feelings can have the opposite effect. Professional help should be sought if there is reason for serious concern. Sources of help include pediatricians, child psychiatrists, "hot line" services, local medical societies, and other physicians.

Many medical organizations recommend that parents join children in viewing television broadcasts about suicide to discuss their feelings afterward. Most important, if you child ever talks about committing suicide, don't dismiss the youngster's comments. Deal with his or her concerns in an open manner. Take action promptly.

WRONGFUL LIFE AND WRCNGFUL BIRTH: NEW LEGAL/ETHICAL TWISTS IN PEDIATRICS

During the past five years, legal precedents have been set that broaden a physician's legal obligation to recognize foreseeable birth defects.

These kinds of suits, which stem from actions usually called wrongful life or birth, will affect all doctors, but particularly pediatricians, says a report in the January issue of Pediatrics, the journal of the American Academy of Pediatrics.

James Caplan, M.D., from the Department of Pediatrics at the State University of New York, Upstate Medical Center, Syracuse, notes in his article that pediatricians are most likely to see patients with genetic, teratogenic or chromosomal disorders.

Wrongful birth, or recovery for damages because of a failed abortion or sterilization, is one type of action in which parents of unplanned by healthy children have been granted the right to sue.

"The extent of the parents' recovery varies from jurisdiction to jurisdiction, depending upon whether the courts have seen fit to offset damages by an amount representative of the 'benefit' bestowed upon the parents by the child's birth," Dr. Coplan explains.

Since physicians have a clearly defined obligation, not just to advise screening procedures on the basis of parental risk history, but also to recognize foreseeable or potentially recurrent clinical syndromes in children or their parents, "genetic malpractice" has now become a medical issue, says Dr. Coplan.

More commonly known as "wrongful life," in which parents of children suffering from a genetic or chromosomal disorder may sue when a physician fails to counsel in a timely fashion regarding risks, this action is for damages for having been wrongfully brought into existence, says Dr. Coplan.

The Syracuse pediatrician concludes it is unreasonable for general pediatricians to recognize all genetic or teratogenic disorders (which number in the thousands). However, appropriate consultations for potential disorders should be made, and for certain generic disorders, every doctor should make a formal evaluation.

These circumstances include such pre-birth disorders are: recurrent fetal wastage, chronic maternal illness or family history of anomalies.

AMERICAN COLLEGE OF PHYSICIANS



GUIDE FOR ADULT IMMUNIZATION ANNOUNCED BY NATIONAL MEDICAL SOCIETY

A handbook that will help physicians meet the vaccination needs of adult patients has been published by the American College of Physicians (ACP), the 60,000 - member national medical specialty society.

Joining the ACP to speak about their efforts to

promote adult immunization were representatives of the National Institute of Allergy and Infectious Diseases (NIAID) and the Centers for Disease Control (CDC).

"The routine immunization of children has virtually eliminated many vaccine-preventable diseases in the United States," said ACP Executive Vice President Robert H. Moser, MD, FACP. "Unfortunately," he continued, "this does not guarantee the disappearance of diseases like tetanus and rubella, and many of the cases we still see are among adults."

According to the ACP's Guide for Adult Immunization, 88% of hepatitis B cases reported with known ages in 1982 occured in people older than 20. An estimated 20% of young adults are not immune and may be susceptible to measles, a disease which leads to greater complications for adults than for children. And although the number of cases of tetanus has dropped sharply in the United States, the ACP notes that of the 75-plus cases per year that do occur, virtually all are in adults who have not been properly immunized.

"Childhood immunization programs have given us a goal to mimic, "Dr. Moser said, adding that "Immunization isn't just kid stuff. There are safe, effective vaccines against a number of diseases that we see in adult patients. We want every physician to get in the habit of routinely considering what vaccines would protect patients against these diseases."

The National Institute of Allergy and Infectious Diseases has long been involved in developing new vaccines and improving already existing ones. One of the first vaccines developed by the Institute was the live adenovirus (types 3, 4 and 7) vaccine, now used by the armed forces to control acute respiratory disease in new recruits. The NIAID was involved in developing and testing various influenza vaccines and continues to work toward an improved, live attenuated vaccine for the disease. The Institute also participated in the development of a hepatitis B vaccine and had a major role in reviving the vaccine against pneumococcal pneumonia.

In addition to this emphasis on research and basic science, NIAID recognizes the importance of educational efforts such as the ACP's guide. "The Institute supports efforts to educate health professionals and the general public about the safety and efficacy of vaccines for adults," said NIAID Director Anthony S. Fauci, MD, FACP.

The ACP's Guide to Adult Immunization was written to help physicians give optimal care by preventing —rather than just treating— disease. The guide discusses clinical issues related to specific vaccines and gives recommendations for immunizing adults based on age, health and special considerations such as lifestyle, occupation and environment.

"These conditions determine the infectious diseases a patient is at greatest risk of contracting, and thus should be immunized against," said Theodore Eickhoff, MD, FACP, chairman of the committee that developed the guide. For example, people with diabetes or cancer, pregnant women, travelers and health care personnel all have special vaccine needs. The ACP's guide is organized according to these categories as well as by vaccines so a physician can quickly identify the needs of each patient.

The immunization needs of the American public also have been addressed by the Centers for Disease Control (CDC), part of the Public Health Service of the US Department of Health and Human Services. Charged with preventing unnecessary illness and death and enhancing the health of Americans, the Centers coordinate national preventive health programs with state and local health agencies and work to investigate and control infectious diseases.

The CDC recently released its own set of recommendations for the immunization of adults, to which the ACP contributed through liaison representative Dr. Theodore Eicknoff. According to Alan R. Hinman, MD, FACP, director of the Division of Immunization of the Center for Prevention Services and CDC liaison with the ACP Committee on Immunization, "the reciprocal cooperation of the ACP and the Public Health Service

and its Immunization Practices Advisory Committee (IPAC) in developing recommendations for the immunization of adults represents a necessary beginning to our joint efforts to improve the protection of our adult population".

The ACP's guide includes a reference table summarizing the College's recommendations and an appendix of currently licensed vaccines listed with their manufacturers and license numbers, date of license and prices as of mid-1984. Several tables —such as a summary outline of vaccines to be considered for specific groups— are available for quick reference. Of particular use to the practicing physician is a prototype immunization history form that can be reproduced for use in patient files. To keep up with the manyadavances in vaccine practices, the ACP plans to issue an updated version as needed or every two to three years.

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MOTHERS TRANSMIT AIDS TO INFANTS

Infants who have acquired immune deficiency syndrome (AIDS) probably got the infection from their mothers before birth, according to Gwendolyn B. Scott, MD, and colleagues of the University of Miami School of Medicine.

Writing in JAMA, the researchers describe the clinical and immunologic characteristics of 16 mothers of 22 infants with AIDS or AIDS-related complex. At the time of delivery, 15 of the 16 mothers appeared healthy, but tests revealed immune system abnormalities. Within a 30-month follow-up period, five of the mothers developed AIDS, and seven developed AIDS-related complex, the researchers report.

"These observations do not clarify the source of infection in the mother, but they support the argument that infant cases most likely result from infection transmitted from the mother rather than from other household members," they say. The infants developed symptoms of AIDS at a mean age of 4 months, which suggests an in utero or perinatal transmission, and perhaps increased susceptibility to the disease.

The researchers note that 12 of the 16 mothers were Haitian, three reported using intravenous drugs and one acknowleged prostitution. One mother had had a blood transfusion two years before giving birth.

Among other findings: an asymptomatic mother can have more than one affected offspring, and some mothers may develop AIDS two to four years after the birth of an infant with the disease. The researchers report than six of the mothers with immunologic abnormalities had infants without any evidence of AIDS.

Despite the persistence of immunologic abnormalities, four of the mothers have remained outwardly healthy. The researchers say this suggests that the infection that causes immune dysfunction may not inevitably result in clinical disease.

JAMA, Jan. 18, 1985

CDC SAYS VACCINE CAN PREVENT BACTERIAL INFECTION

The number of cases of Hemophilus influenzae type B (HIB), which affects thousands of children each year, can be reduced substantially by using a safe, available

vaccine, according to a report in JAMA.

Stephen L. Cochi, MD, and colleagues at the Centers for Disease Control in Atlanta say the polysaccharide vaccine is both cost-effective and efficacious: routine vaccination of children at 18 or 24 months would prevent more than 2,500 cases of HIB each year. The disease affects one in 200 children in the United States annually, accounting for approximately 12,000 cases of bacterial meningitis and 7,500 cases of other serious illness.

The researchers say that direct savings can also be realized (as much as \$4.2 million in the short term) if vaccination for HIB is included with the routine visit and immunization for DTP at 18 months. An optional second dose at 24 months, especially for children attending day care centers, would increase the efficacy of the vaccine.

In a related editorial, Joel I. Ward, MD, of UCLA School of Medicine in Torrance, Calif., says one problem with the vaccine is that it is most effective in children older than 24 months, yet approximately 75 percent of HIB cases occur in younger infants. Ward recommends vaccinating children aged 24 months and older. "With this strategy there may be increased costs for immunization and concerns about lower immunization rates, but the reassurance about (vaccine) efficacy at 24 months of age should be paramount." The vaccine is not protective in infants younger than 12 months, Ward says, and is of questionable efficacy in those aged 12 to 23 months. He adds that a protein conjugate vaccine may be developed soon that would be effective in infants.

Ward agrees that immunization for HIB is most important for children who attend day care centers. The CDC researchers note that for children 18 months and older, 66 to 70 percent of all systemic HIB cases in the United States are attributable to exposure in day care centers.

JAMA Jan. 25, 1985

LEAD EXPOSURE RELATED TO HIGH BLOOD PRESSURE

Blood-lead levels well below the usually designated "toxic level" are associated with increased blood pressure, according to a national study of thousands of adolescents and adults reported in JAMA.

The study, conducted between 1976 and 1980, found a direct relationship between blood lead levels and high blood pressure in both black and white men and women aged 21 to 55 years. This relationship was not found to be significant in persons 56 to 74 years old.

William R. Harlan, MD, and colleagues from the Schools of Medicine and Public Health at the University of Michigan, Ann Arbor, note that the effects of intense and prolongued lead exposure have been known for many years. They say interest has recently shifted to possible harmful effects of lead at lower levels of exposure that are commonly found in the general population. Additional interest in the relationship between lead and blood pressure has expanded to include attention to the relationship of calcium and zinc intake and blood

pressure.

Their study found that serum zinc levels were significantly lower for older hypertensive women and for older men who had high systolic readings. In younger persons, serum zinc tended to be higher, but not significantly higher, in hypertensives.

Dietary calcium intake was significantly lower in both male and female young persons with hypertension; in the older group dietary calcium was significantly lower only for hypertensive women.

The researchers note that the relationship of blood lead to blood pressure "has clinical relevance." Early observations of toxic effects on the cardiovascular system include increased incidence of stroke or renal impairment following heavy industrial exposure. Hypertension has also been found in persons who have consumed lead-containing moonshine whiskey.

Between 1976 and 1980, the study period, the researchers found a 37 percent decline in blood lead levels. They call alkyllead gasoline additives "a major alterable source" of atmospheric contamination for the general population. During this period, lead additives to gasoline were reduced as was total consumption of all automotive gasoline.

The researchers conclude that their cross-sectional analyses of the blood pressure effects of lead, calcium and zinc should not lead to inferences of causality, although their observations are consistent with extensive animal studies of lead toxic effects and trace metal interactions.

JAMA Jan. 25, 1985

FLULIKE SYMPTOMS CAN SIGNAL CARBON MONOXIDE EXPOSURE

Headache and flulike symptoms can be clinical sings of exposure to deadly carbon monoxide fumes, say physicians writing in the January Archives of Ophthalmology. Lance S. Ferguson, MD, and colleagues from the University of Cincinnati Medical Center tell of five family members exposed to an improperly ventilated heating unit. Two died as a result of exposure, one suffered severe visual loss resulting from retinal hemorrhages and other damage caused by carbon monoxide intoxication, and two regained full consciousness and health. They reported a five-day history of headache and flulike symptoms prior to losing consciouness. "Had they been examined during this period, recognition of these hemorrhages may have averted the tragic consequences of this incident," the authors say.

FIND 'NATURAL' BOUNDARY FOR SCHIZOPHRENIA

There is a natural boundary in symptoms that distinguish schizophrenic patients from other psychiatric patients as well as from normal controls, according to a new study in the January *Archives of General Psychiatry*. C. Robert Cloninger, MD of the Washington University, School of Medicine in St. Louis, and colleagues studied

about 2,000 subjects for 12 years. More than 68 percent of schizophrenic patients had two or more of four clearly defined syndromes: delusions of persecution; delusions of control; mood-incongruent delusions; and auditory hallucinations. Less than 2 percent of nonschizophrenic patients had two or more of the syndromes. "Scale scores were valuable for quantifying the certainty of diagnosis and predicting outcome," the researchers say.

EARLY TEST DETECTS IRON DEFICIENCY

One part of a routine automated blood cell count can be used as an early indicator of iron deficiency, according to a report in JAMA. Variation in the size of red blood cells, measured as red blood cell distribution width (RDW), seems to occur before any other abnormalities associated with iron deficiency.

At the University of Texas Medical Branch, Galveston, Suzanne McClure, MD, PhD, and colleagues studied blood samples from 163 nonanemic patients; 90 had normal RDW values, and none of these had a serum iron saturation below 20 percent. Seventy-three patients had increased RDW, and 48 of these patients had a serum iron saturation below 20 percent. "An abnormal RDW in an otherwise normal blood cell count appears to be a highly sensitive (48/48) indicator of early iron deficiency," the researchers say.

Before anemia becomes apparent, early iron deficiency may be suggested by a low mean cell volume, the researchers note, but before the cells become small, there is variation in the size of the cells produced. The study also showed that as iron deficiency developed in 13 patients with abnormally high levels of red blood cells, their RDW increased a minimum of four weeks before mean cell volume changed.

"Thus, except in rapid, intentional phlebotomy, it appears that RDW becomes abnormal earlier in the development of iron deficiency than do any other values in the automated blood cell count," the researchers say. They add that this is partly due to the addition of progressively smaller red blood cells to the blood as iron deficiency worsens.

The researchers note that an increased RDW may also be caused by nutritional deficiencies, by transfusion of red blood cells of a different size, or by cytotoxic chemotherapy. Most cases, however, indicate iron deficiency, and the test is available in many hospitals as part of a routine automated blood cell count.

JAMA Feb. 15, 1985



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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

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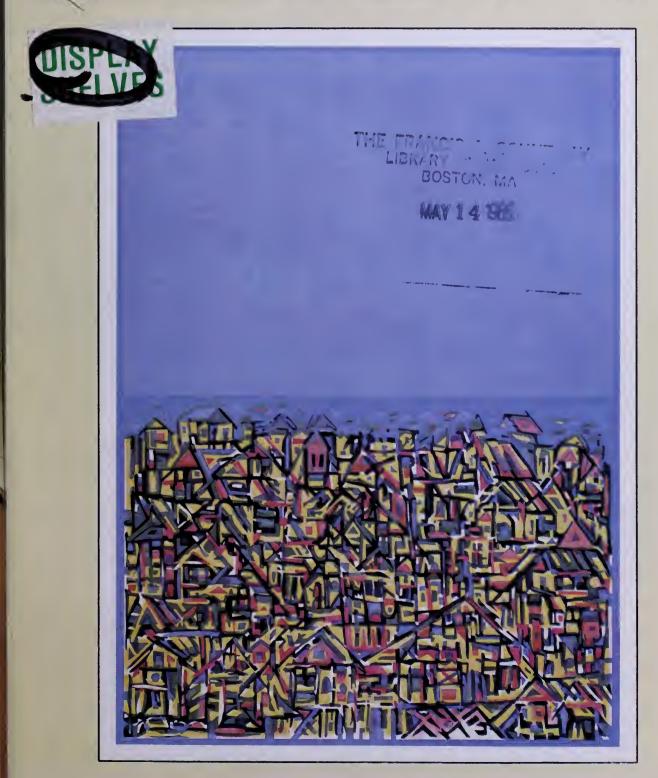
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Columna del Editor



s por todos conocido la relevancia del Síndrome de Inmunodeficiencia Adquirida (SIDA o AIDS) en la medicina actual y la importancia que han tenido sus consecuencias en la sociedad en esta parte final del siglo XX. Su dimensión ha sido una de carácter mundial y Puerto Rico no ha sido excepción, habiéndose confirmado cerca de 150 casos de SIDA hasta principios de 1985. Se espera que esta incidencia aumente comparativamente con la de 1984. Es por ello que debe destacarse en este número del Boletín el artículo del Dr. Carlos Ramírez Ronda. En él se recomiendan las medidas de precaución que deben tomarse cuando se entra en contacto cercano con pacientes de SIDA durante el manejo de los mismos. El autor hace recomendaciones específicas y se establecen las normas a seguir cuando se participa en el cuidado de estos enfermos. Su valor práctico es enorme y debe ser lectura obligada para todos.

Hemos recibido gran variedad de comentarios con relación al Editorial del mes de Febrero donde se comenta sobre el problema del Centro Médico de Puerto Rico y menciona el editorialista varias alternativas que en su opinión pueden ser soluciones a un problema de 20 años de existencia. La Junta Editora quiere aclarar una vez más que estos comentarios editoriales no necesariamente reflejan el sentir, ni pretenden ser, un endoso de la Asociación Médica de Puerto Rico a los puntos de vista del autor. Sí creemos que son puntos controversiales pero bien traidos y con intención de resolver, no de criticar y mucho menos ofender posturas establecidas por más tambaleantes que se encuentren. La actitud más correcta y constructiva la ejemplariza el Dr. José M. Torres-Gómez quien nos somete sus reacciones y opiniones por escrito y la Junta Editora las publica para provecho de todos los que genuina y desinteresadamente nos preocupamos por algo tan intimamente ligado a nuestro trabajo diario, que es del pueblo de Puerto Rico, para el pueblo de Puerto Rico y que no está cumpliendo su cometido.

Kiraimii 5mo

Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico



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NUESTRA PORTADA

Arrabalito. Serigrafía de Carmelo Sobrino. El artista nació en Manatí en enero de 1948. Estudió en la Escuela de Artes Plásticas del Instituto de Cultura y en la Academia San Carlos, de México. Es fundador del Taller Capricornio y co-fundador del Taller Alacrán. Se ha destacado en el grabado y ha expuesto en el Museo del Grabado del Instituto de Cultura Puertorriqueña, el Ateneo, y el Museo del Barrio en Nueva York. Ha participado en la Primera Bienal del Grabado Internacional en Buenos Aire (1972), la Bienal de Sao Paulo, la exposición Exxon de Nueva York y la Bienal de San Juan del Grabado Latinoamericano (1974).

La Asociación Médica de Puerto Rico agradece al autor el permitir el uso de su obra en nuestra portada. También va nuestro agradecimiento al Dr. Bernardo Marqués quien nos cedió su serigrafía para hacer posible la publicación de la misma en nuestra revista.

EDITORIAL

Implicaciones Económicas: El Síndrome de Inmunodeficiencia Adquirida

l Síndrome de Inmunodeficiencia Adquirida (SIDA) ha tomado un lugar prominente en las enfermedades del siglo XX. Desde 1981 en los Estados Unidos de América se han diagnosticado sobre 8,000 casos. Esta condición se ha diagnosticado en todo el mundo y hay más de 500 casos en el continente Americano, 600 casos en Europa y varios miles en Africa.7 En Europa, en un período de 8 meses, el número de casos se duplicó.9 Estudios epidemiológicos anticipan que en los próximos dos años en los E.E.U.U. se diagnosticarán 40,000 nuevos casos. 4 Conociendo que el período de incubación es entre 6 meses y cuatro años y que la prevalencia de infección con HTLV-III (Human T cell Lymphotropic Virus III) es sobre el 80% en grupos seleccionados de alto riesgo, se puede anticipar un continuado aumento exponencial de SIDA. Con una tasa de mortalidad que excede el 80% a los dos años después del diagnóstico, esta condición toma una posición de suma importancia como la más seria epidemia de los tiempos modernos.6

En Puerto Rico, SIDA ha sido diagnosticado en sobre 130 pacientes hasta diciembre de 1984, y 57% de éstos han muerto de su enfermedad. La experiencia en Puerto Rico ha sido publicada en reportes de instituciones.² El problema serio que se presenta es que en el momento hay un número significativo de personas (sobre 150) en las cuales se sospecha SIDA y están bajo estudio en el Centro Latinoamericano para Enfermedades de Transmisión Sexual. En los hospitales afiliados a la Escuela de Medicina de la Universidad de Puerto Rico, Hospital Universitario, Hospital de Veteranos y Hospital Municipal, hay siempre algún paciente hospitalizado con la condición y en el Hospital Universitario han tenido hasta 7 pacientes con SIDA hospitalizados a la misma vez.

El impacto económico de esta condición es grande y tiene repercusiones en el nivel local hospitalario y a nivel estatal como un problema de salud pública. Se ha estimado que el costo del cuidado médico de cada paciente con SIDA excede \$50,000 y el costo de cada paciente con una condición relacionada a SIDA en \$2,000.00.³ El impacto presupuestario para cualquier hospital es enorme; en instituciones como el Hospital Universitario, el Hospital Municipal y el Hospital de Veteranos, los

cuales admiten un mínimo de 10 pacientes con SIDA al año y se puede predecir que el Hospital Universitario en 1985 admitirá entre 40-60 pacientes, el costo para esta institución sobrepasa los 2 millones de dólares. Si en Puerto Rico se diagnostican entre 60-80 pacientes nuevos en 1985, el impacto económico mínimo es de 4 millones de dólares y éste es un cálculo conservador, ya que si utilizamos las predicciones derivadas de estudios epidemiológicos,4 en los próximos dos años aquí se diagnosticarían hasta 400 casos nuevos. El impacto económico no cesa con los casos, sino que se estima un gasto de \$2,000.00 por cada individuo que se estudia bajo sospecha de SIDA, y próximamente se añadirá el costo del cernimiento de los productos sanguíneos para anticuerpos en contra de HTLV-III. Se estima que costará \$5.00 por cada unidad de sangre que se procese; no hace falta una calculadora para determinar el impacto económico en las finanzas de los sistemas de salud.5, 8

El problema que enfrentamos entonces es cómo planificar de tal manera que el impacto económico de esta condición pueda canalizarse y que los recursos humanos se utilizen en la mejor manera posible. Las avenidas son varias y dependen de los recursos fiscales disponibles. ³ En algunos lugares de E.E.U.U. se han creado unidades para el cuidado de los pacientes con SIDA; si los fondos están disponibles han funcionado inicialmente más en vista del aumento en los casos en una forma logarítmica la demanda por servicios han sobrepasado la capacidad y los recursos fiscales no son suficientes. La otra alternativa es distribuir la carga económica de estos casos de tal manera que este tipo de paciente pueda admitirse en hospitales privados o públicos y tener en varias regiones facilidades médicas para admitir estos pacientes. Esto permite que el paciente con SIDA no se disloque de su familia y ambiente social por tener que recibir tratamiento médico lejos del área que reside. En Puerto Rico, por ejemplo, se puede tener facilidades hospitalarias en San Juan, Bayamón, Ponce, Mayagüez, Humacao y Caguas; en todas estas áreas hay la infraestructura necesaria para el cuido adecuado de estos pacientes. El segundo problema al cual nos enfrentamos es para el rastreo, cernimiento y diagnóstico de casos en los cuales

se sospecha SIDA. El diagnóstico de SIDA requiere que el médico domine los criterios epidemiológicos, al igual que domine la interpretación de pruebas inmunológicas y sea entrenado en la especialidad. El sistema establecido de un lugar en donde toda persona en la cual se sospeche SIDA sea evaluada por un especialista en un lugar centralizado, es efectivo y provee al paciente una evaluación por expertos en una forma rápida. El sistema establecido no es perfecto, funciona, más necesita reforzarlo. Lo que debemos prever es que la demanda por evaluaciones aumentará una vez esté disponible la prueba de ELISA para anticuerpos en contra de HTLV-III. El sistema debe de fortalecerse con más personal y el sistema de referido para tratamiento cuando sea necesario agilizado para que la carga económica de estos pacientes se distribuya dentro del sistema de salud, especialmente en nuestro país donde los recursos económicos son limitados.

El impacto económico de SIDA es enorme y aumentará y puede convertirse en un monstruo sin contención, especialmente si SIDA se extiende a grupos fuera de los grupos de alto riesgo y si no se planifica dentro de la realidad fiscal de nuestro pueblo. Escoger entre el sistema centralizado de hospitalización versus el sistema de distribución por región lo determinará nuestros recursos fiscales.

(allemental on D. FHED)

Carlos H. Ramírez-Ronda, M.D., F.A.C.P. Profesor de Medicina Director, Programa Enfermedades Infecciosas Escuela de Medicina Universidad de Puerto Rico

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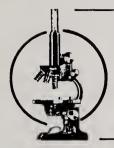
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PATHOLOGYReview

María Castillo-Staab, M.D.

Este es el caso de un hombre de 55 años con historial de visión borrosa del ojo derecho de un año de duración. El examen oftalmológico reveló desprendimiento de la retina y un tumor en la cámara posterior. Al paciente se le practicó enucleación del ojo derecho y el hallazgo patológico se ilustra en la figura 1.



Figura 1. Espécimen quirúrgico. Ojo derecho enucleado.

¿CUAL ES SU DIAGNOSTICO?

- A. Retinoblastoma
- B. Carcinoma de Células escamosas
- C. Melanoma de la Coroides
- D. Quiste parasitario
- E. Desprendimiento espontáneo de la retina

Departamento de Patología, Escuela de Medicina, Universidad de Puerto Rico, Río Piedras, Puerto Rico

Melanoma de la Coroides

El melanoma representa el tumor maligno intraocular más común en adultos de la raza blanca. El 70% de todos los tumores malignos de los ojos son melanomas. La incidencia de este tumor es de un caso por cada 2,500 personas blancas en la población de los Estados Unidos.

En Puerto Rico el Registro de Cáncer para el año 1982 informa un caso de melanoma intraocular en 6,236 casos nuevos de cáncer registrados por localización anatómica, sexo y edad. La edad promedio es de 55 años, ocurre con más frecuencia en el hombre y es muy rara su aparición en personas de raza negra. El 73% de los melanomas oculares se originan en la coroides. Pueden originarse también del iris, cuerpos ciliares, disco óptico y conjuntiva.

El síntoma incial más común es la visión borrosa. La mayoría de estos tumores, sin embargo, se encuentran en exámenes oftalmológicos rutinarios en pacientes asintomáticos.

EL comportamiento biológico de los melanomas oculares depende de su localización anatómica, del patrón de crecimiento (circunscrito o difuso), del patrón histológico y del tamaño de la lesión.

Los melanomas del iris y conjuntiva suelen producir manifestaciones clínicas temprano y son fáciles de reconocer por su localización, pero la mayoría de los melanomas ocurren en la cámara posterior y en el segmento superior.

El tamaño del tumor es también de gran importancia para el pronóstico. Los pacientes con tumores que miden menos de 1cm al momento de la enucleación tienen mejor pronóstico que aquellos que presentan lesiones mayores de lcm. Los melanomas de la cámara posterior tienden a crecer en forma de "hongo" y el tumor presenta usualmente, buena vascularidad y necrosis.

Los melanomas tienden a extenderse fuera de la órbita, invadir el nervio óptico y producir metástasis a distancia.

Histológicamente los melanomas se originan de los melanocitos, que son células pigmentadas de las distintas estructuras oculares. Las variantes histológicas dependen del tipo de célula que componga el tumor.

Se describen tres variantes: las de células fusiformes (Fig. 2) las de células epitelioides y las mixtas, siendo la variante de células mixtas la más común (45%).

El grado de pigmentación varía de célula a célula, y de tumor a tumor. Los tumores más pigmentados tienen mejor pronóstico que las lesiones menos pigmentadas. Los melanomas de la variante fusiforme tienen mejor pronóstico que los de la variedad epitelioide.

El mejor método para hacer un diagnóstico de melanoma intraocular es con un examen concienzudo del fondo de ojo, con luz indirecta. Otros métodos utilizan ultrasonido, angiografía con fluoresceína, fósforo radioactivo y pruebas inmunológicas.

El tratamiento, si los tumores son pequeños o medianos, suele ser enucleación, seguido o no de radioterapia y/o quimioterapia.

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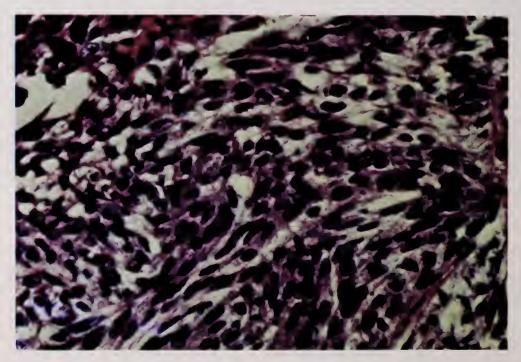
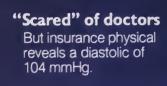


Figura 2. Células fusiformes arregladas en haces. Detalle histológico.



What can you do for hypertensives like Janet M?



Career woman
At her peak at
50...no room in
her busy schedule
for a complicated
regimen.

Eats out
Will try from now
on to select dishes
with fewer calories.

Childhood asthmatic Hasn't wheezed in forty years.

Patient description is a hypothetical composite based on clinical experience and evaluation of data

Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Janet M represents 4,533 women age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Lessens risk of bronchospasm

Propranolol use has been associated with bronchospasm even in patients with no history of wheezing or dyspnea. Unlike propranolol, TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

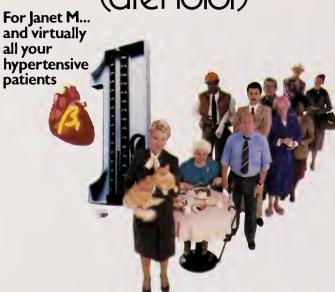
The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy!



For Janet M...and virtually all your hypertensive patients

TENORMIN® (atendol)





TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2²-hydroxy-3²-[1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266 fit is a relatively polar hydrophilic compound with a water solubility of 26 5 mg/ml at 37 C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C), and less soluble in chloroform (3 mg/ml at 25°C).
INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thearde-tive diviser.

Sion. It may be used alone for concominantly with other anunypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenoloi slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn. Schemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawn symptoms occur.

drawal symptoms occur Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, how-ever, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta;-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia if treatment is continued, care should be allowed to elapse between the last dose and anesthesia if treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg. dobutamine or isoproterenol with caution—see OVERDOSAGE) Manifestations of excessive vagal tone (eg. profound bradycardia, hypotension) may be corrected with atropine (1-2 mg l·V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyrotoxism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg. reseptine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or posturial hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonding.

of clonidine

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies.support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol-kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo / fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

atencial Pediatric Use: Safety and effectiveness in children have not been established
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg., by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is smilar causal relationship is uporquine.

is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects)

from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).
[2%-1%), leg pain (0%-0.5%).
CENTRAL NERVOUS SYSTEM: NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) whee ziness (0%-0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM: NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), tatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), nausea (3%-1%)
RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered it any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.
POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and laces there there progressing to consider the progression of time and laces there there progressions.

bances, hallucinations, an acute reversible syndrome characterized by discrientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolof has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nore interpretation of the properties of the propert

Creatinine Clearance (ml_min/1 73 m²)	Elimination Half-life (hrs)	Maximum Dosage	
15-35	16-27	50 mg daily	
<15	>27	50 mg every other day	

Patients on hemodialysis should be given 50 mg affer each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolor) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolor) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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ESTUDIOS CLINICOS

Kidney Transplantation in Drug-Addicts

Sooho Cho, M.D. Luis H. Toledo-Pereyra, M.D., Ph.D. James I. Whitten, M.D. Vijay Mittal, M.D. Robert Allaben, M.D.

Abstract: In a restrospective analysis of our kidney transplant patient population we noted that those recipients that were drug-addicts had improved graft survival (74% one year) when compared to the non drug-addict group of patients (46% - one year). Patient survival was similar for both groups. The actual reasons for the improved graft survival in drug-addicts are not yet clearly determined, even though the alteration of the immune response appears to be the most important factor. In short, in our patient population, drug abuse is not, at the present time, a risk factor for kidney transplantation.

Prug abuse remains a controversial issue when evaluating patients requiring kidney transplantation for end stage renal disease (ESRD), 1-4 particularly in view of the fact that nephropathy may be associated with heroin abuse. 2,5 Most centers, in general, agree not to transplant drug-addicts, especially in view of the organ shortage recently identified. 6 The purpose of this study is to evaluate a group of drug-addicts that received kidney transplantation for the treatment of their ESRD.

Materials and Methods

The entire patient study group consisted of 200 renal transplants performed at Mount Carmel Mercy Hospital between May 1979 and April 1984. Patient records were retrospectively reviewed and transplant recipients were divided into two groups: 1) drug-addicts and 2) non drug-addicts. Of these, twenty patients had a history of drug-addiction (heroin, n=14; cocaine, n=6), ranging from 1 to 23 years, and received twenty two kidney transplants, with 19 first and 3 second transplants. During the time that they were being considered for transplantation, all patients were required to terminate their use of drugs and be approved by a special committee at our center; only six were identified as nonusers at the time of evaluation. All patients were males and ranged in

age from 19 to 62 years $(33.3 \pm 10.2 \text{ (M} \pm \text{SD)})$. Fourteen patients were black and six patients were white. Fourteen patients received chronic hemodialysis from 1 to 72 months $(33.4 \pm 19.7 \text{ (M} \pm \text{SD)})$. The other six patients were hemodialized for less than one month prior to transplantation. None of the patients underwent splenectomy or nephrectomy prior to transplantation. In one patient, the kidney, as well as pancreas, were transplanted simultaneously.

The non drug-addict group was comprised of 178 patients who received 139 first, 22 second, and 3 third cadaver renal allografts, as well as fourteen patients who received living related grafts. In the drug-addict group the causes of renal failure were: hypertension (4 patients), and polycystic kidneys (1 patient). Similar etiology as the cause of renal failure was identified in the non drug-addict group. In all cases, the abused drug appeared to play a minor, rather than a major role in the etiology of ESRD.

Twenty one of the 22 renal allografts in the drug-addict group, were from cadaveric donors and one was from a living related donor. Of these donors, 15 were males and 7 were females; 5 grafts matched for 1 HLA antigen, 4 matching for 2 or more HLA antigens and the rest did not show any HLA antigen matching. The age of the donors ranged from 2 to 52 years (29.0 \pm 13.2 (M \pm SD)).

Our methods of procurement, harvesting, donor management, and preservation have been published and were the same for both groups. Our transplantation technique and immunosuppressive therapy have also been reported previously.8,9 No compulsory blood transfusion protocol was followed for neither group. During the period of this study, the primary immunosuppressive treatment consisted of prednisolone, azathioprine and antilymphoblast globulin (ALG) (or antithymocyte globulin, ATGam, UpJohn) (n=190) or cyclosporine (n=10). Multiple antibiotics (ampicillin, cleocin and gentamycin) or cefotaxime alone were used as prophylactic preoperative antibiotics. Minnesota horse antilymphoblast globulin (ALG) or antithymocyte globulin (ATGam, UpJohn), or methylprednisolone sodium succinate were utilized to treat rejection episodes.9

Graft failure was defined as the need for dialysis at anytime during the transplant course. All patients were

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followed weekly or monthly in the outpatient clinic. The follow-up period in this study ranged from 6 to 60 months (26.7 \pm 16.3 months (M \pm SD)). Graft and patient survival was calculated according to actuarial methods. Chisquare analysis was used for statistical comparisons.

Results

Figure 1 shows the actuarial graft and patient survival of the patients who underwent kidney transplantation at our center. One year actuarial graft survival for drugaddicts and non drug-addicts was 74 percent and 46 percent, respectively. These differences were statistically significant (p<0.025). However, patient survival, observed in these two groups, 94 percent for drug-addicts and 85 percent for non drug-addict group (ν >0.05), was not significantly different.

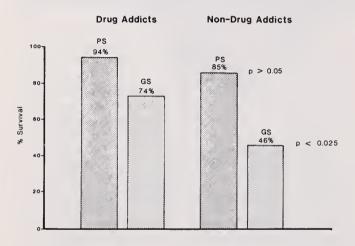


Figure 1. Comparison of 1 year actuarial graft and patient survival of drug addicts and non-drug addicts in kidney transplantation at Mount Carmel Mercy Hospital. A significant difference in the 1 year actuarial graft survival rate was observed between drug addicts and non-drug addicts (p < 0.025). However, the one year actuarial patient survival rate was not statistically different between the two groups (p > 0.05).

Discussion

This retrospective study regarding drug addicts and kidney transplantation at our center demonstrated that these particular kind of patients had improved graft survival as compared with that of non-drug addicts. These findings are similar to those of Sreepada, et al,² and Stevens, et al,³ (Table I). Their studies of heroin addicts who received kidney allografts showed that there was improved graft and patient survival when drug addicts abstained from active drug abuse. The morbidity associated with both groups was not significantly different, even though the non drug-addict group had a higher number of posttransplant complications. The type of infections occurring after transplantation was similar in both groups. Also, no significant differences were noted in the causes of death encountered in either group.

It is interesting to note that in our patient population the improvement of graft survival was not necessarily associated with discontinuance of the drug after transplantation, since many patients continue to use drugs in spite of active therapy sessions.

TABLE I

Selective Review of Literature Regarding Drug-Addiction and Kidney Transplantation

Author (year)	Number of Transplant Patients	Type of Drug Addiction	*I yr. GS	**1 yr PS
Sreepada, et al (1978)	11	Heroin	64%	73%
Stevens, et al (1983)	15	Heroin	75%	100%
Cho, et al (1984) Present study	20	Heroin, Cocaine	74%	94%

^{*} GS± graft survival

The actual reasons for the improved graft survival in drug-addicts are not yet clarly determined. Many immunological factors such as the altered immune response in drug addicts and the immunosuppressive effect of the drug used may be considered. Perhaps further controlled studies from other centers will provide more information regarding the actual prognosis in drugaddicts following renal transplantation. Based on our limited number of cases, we believe at the present time that drug abuse does not appear to be a risk factor for kidney transplantation.

Resumen: En un análisis retrospectivo de nuestros pacientes de transplante de riñón, notamos que los pacientes que eran drogadictos tuvieron una sobrevida del injerto (74% un año) mejor que los pacientes que no eran drogadictos (46% un año). La sobrevida del paciente fue similar en los dos grupos. Las razones por las cuales la sobrevida del drogadicto fue mejor no se entienden muy bien, aun cuando la alteración immunológica es el factor más importante. En resúmen, parece que la drogadicción no es un factor the riesgo elevado para el transplante de riñón.

Acknowledgement

The assistance of Debra Gordon in the preparation of this manuscript is appreciated.

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^{**}PS ± patient survival

The Value of Image Post-Processing In Sonomammography: A Preliminary Report

Bernardo J. Marqués, M.D.* Manuel R. Pérez, M.D.* Glennys Alvarado, R.D.M.S.*

Summary: Manual, computer-assisted post-processing manipulation of gray-scale segments of accessed images during sonomammography makes it possible to isolate, for detailed analysis, the capsule of cystic lesions of the breasts. The thickness and uniformity of the capsule can then be evaluated for the presence of focal areas of thickening or intracystic papillary growths. The organization of the breast tissues inmediately surrounding these lesions can also be seen to greater advantage than would otherwise be possible. Cysts with focal areas of capsule thickening or intracystic papillary growths, or those with associated surrounding architectural disorganization can be easily identified for surgical consideration. The potential of post-processing of accessed images in the evaluation of solid breast lesions, is currently under investigation by us and will be the subject of a future report.

Sonomamography is a most valuable diagnostic modality when used to complement the mammographic and clinical examination of the breasts. Determination of the solid or cystic nature of a breast lesion can be easily and reliably established on sonomammography. Although a high Megahertz hand-held transducer is sufficient for the evaluation of a clinically palpable lesion, the total sonographic evaluation of the breast can only be reliably performed with a dedicated whole-breast scanner. Only thus can the entire breast be studied and non-palpable lesions be consistently identified and subjected to analysis, and this without patient discomfort.

In our facilities sonomammography is selectively utilized as a complement to mammography in those patients with dense, dysplastic or predominantly glandular breasts and in those with dominant breast lesions identified clinically and/or mammographically. Utilizing a dedicated, computer-assisted water-path unit (Ausonics, System 1), approximately two-hundred (200) images of each breast are recorded on video-tape for later playback analysis using a combination of 1, 2, 3, or 4 transducers in the longitudinal, transverse, and/or rotational planes. Representative hard-copy films of areas of interest are recorded for the permanent record sent to the referring physician.

Post-Processing Manipulation of the Images

It is know that the images produced in the monitor by the computer as the patient is scanned, contain a much larger amount of information than can readily be perceived. Manual, computer-assisted post-processing of these images renders accesible some of this hidden information by exaggerating the subtle difference in echo strength of adjacent breast structures. Although this gray-scale manipulation has been occasionally used by other authors as an aid to better define the external contour of malignant dominant breast lesions, we have become aware that many other features of breast lesions, both benign and malignant, can be explored and demonstrated with extreme clarity by careful post-processing manipulation of the images.

The Ausonics, System 1 unit is equipped with a powerful post-processing system which allows us to manually control while under direct observation, a particular level of echo return throughout the gray-scale display of an accessed image prior to recording it on Video-tape or hard-copy film. A video-tape recording of the entire post-processing image modification can also be recorded. Five slider controls have each assigned to them a segment of the sixteen levels of the gray scale (See Fig. 1). Slider#1, for example, is given control over the three blackest segments of the gray scale. Moving that slider to the uppermost position gradually converts the blackest elements of the image to a lighter or totally white shade. Other segments of the gray scale can be similarly modified by adjustment of the controlling sliders. Any image of the patient's breast obtained can therefore be modified by changing one or more slider levels. Although initially this manipulation was on a trial and error basis,

SIGNAL STRENGTH LEVELS CONTROLLED BY EACH SLIDER

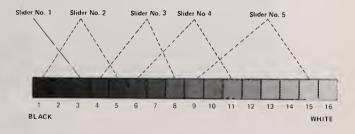


Figure 1. SIGNAL LEVELS OF STORED IMAGE (Coded as Gray Shades)

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particular slider settings have become apparent in the optimal demonstration of specific features of lesions. Once these particular setting patterns are refined, they could be set into the software of the computer and be recalled at will through the computer menu.

Utilizing this post-processing maneuvers we have been able to clearly separate the echoes of a cyst capsule from those of the surrounding breast tissues as well as from the normally imperceptible echoes of the contained fluid. This has allowed us for the first time to see in great detail the capsule of cystic lesions of the breasts making it possible to identify even very small intracystic papillary proyections that would have otherwise been missed. Focal areas of cyst wall thickening as well as generalized thickening of the cyst capsule can easily be identified and measured. The architecture of the surrounding breast tissues is also seen to great advantage with this maneuver.

Cysts with generalized or focal areas of wall thickening, those with papillary intracystic growths and those associated to disruption of the architecture of the surrounding tissues can be identified for surgical consideration (aspiration cytology and/or excision), and those with thin, uniform capsules and preserved surrounding architecture can be identified for periodic followup. Pneumocystography, aspiration or excision of many cysts may thus be avoided.

Regarding solid breast lesions, significant improvement in the amount and quality of sonomammographic information is obtained with post-processing. These findings will be the subject of a future report.

The present report is limited to the sonomammographic evaluation of cystic lesions of the breasts as it is significantly enhanced by the use of manual post-processing technique. (Figs. 2, 3, 4, 5, & 6)

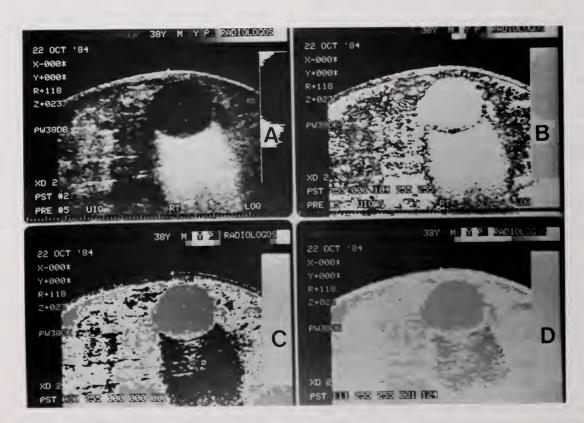


Fig. 2 A. Original image of 3 cm. cyst. Note standard gray-scale at upper left hand corner.

B, C, D. Same image after post-processing with 3 different settings. Note cyst wall separate from cyst content. Note corresponding changes in the gray-scale at upper left of each image.

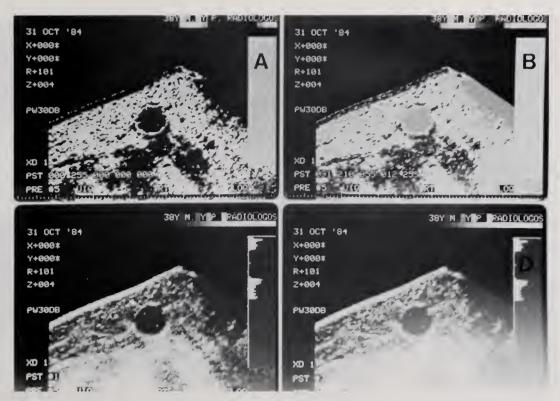


Fig. 3 A and B Post-processed images of 1.5 cm. cyst. Note the excellent visualization of the cyst capsule and the undisrupted disposition of the surrounding breast tissues.
 C & D Original accessed image with standard gray-scales of the equipment.

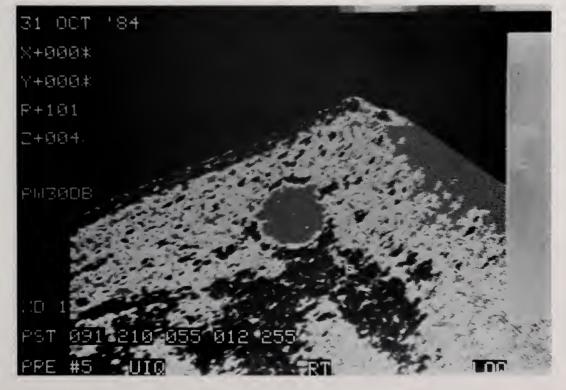


Fig. 4 Close-up view of same case as in Fig. 2. Note the slight irregularity of the cyst wall, several minute folds and a minute incomplete septal structure. Architecture of surrounding breast tissues is seen to advantage. Note the modified gray-scale at upper left corner.

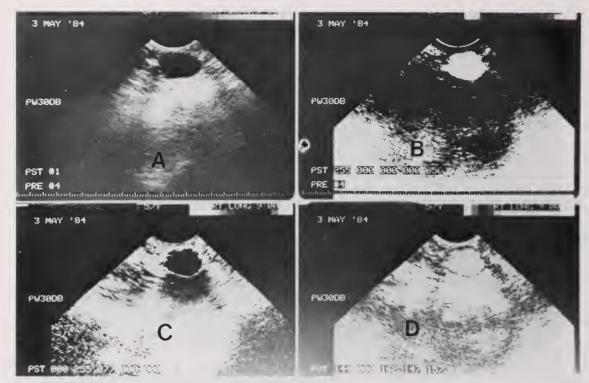


Fig. 5 A. Original image of a 2.5 X 1.8 cm. cyst. Hand-held realtime transducer of the unit used in this case.

B, C, and D. Same image after manual post-processing. Note excellent wall demonstration in C and D and small incomplete septal structure best seen on C. Note gray-scale differences at upper left corner and corresponding slider settings numerically expressed at lower right corner.

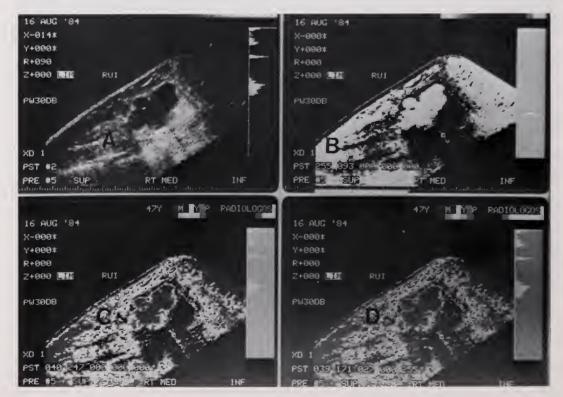


Fig. 6 A. Original image of a cluster of cysts.

B, C and D Same image after post-processing with three different settings. Walls and septal structures seen to advantage on C and D. Irregularity and thickening of posterior wall elements also seen to advantage.

El post-procesamiento manual de segmentos de la escala de grises de las imágenes producidas durante la Sonomamografía ha hecho posible el aislar, para análisis minucioso la cápsula de lesiones quísticas de los senos. El grosor y la uniformidad de esta cápsula puede entonces evaluarse para la presencia de áreas focales de engrosamiento o lesiones papilares intraquísticas. La organización de los tejidos mamarios advacentes a estas lesiones pueden también verse con óptimo detalle tras la manipulación asistida por computadora de estas imágenes. Lesiones quísticas con áreas focales de engrosamiento, aquellas con engrosamiento generalizado de la cápsula, aquellas con crecimiento papilar intra quístico, o aquellas rodeadas por tejidos desorganizados pueden ser identificadas para consideración quirúrgica. El potencial de este post procesamiento manual de imágenes en la evaluación de lesiones sólidas del seno está siendo investigado por nosotros y será el sujeto de un informe futuro.

Acknowledgement

The authors wish to acknowledge with gratitude the help provided by Mr. Gerry Buss, Service Manager of Ausonics Corporation, in our understanding of the image manipulation process.

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ASOCIACION PUERTORRIQUEÑA DEL PULMON

CAMPAMENTO DE VERANO PARA LA EDUCACION Y REHABILITACION DEL NIÑO ASMATICO (V.E.R.N.A.)

Objetivo:

Los Campamentos V.E.R.N.A. tienen como objetivo el educar y promover la rehabilitación de niños que padecen de asma bronquial en Puerto Rico. Para lograr dicho objetivo lleva a cabo actividades educativas, deportivas, recreativas y culturales que ayuden a mejorar la condición física y emocional del niño.

V.E.R.N.A. ¿Para quién?

Los campamentos van dirigidos hacia aquellos niños de ambos sexos con asma que por su severidad limitan significativamente su asistencia a la escuela y su participación en actividades de su edad. Incluye además aquellos niños que requieren visitas frecuentes a Sala de Emergencia o que por su condición se ve afectada la relación del niño con la familia misma. En V.E.R.N.A. se ofrecen los servicios de enfermería todo el tiempo.

Un grupo de médicos especialistas evaluarán diariamente a los niños participantes que así lo requieran.

Cuenta además con un director de deportes dinámico y personal especializado para el desarrollo de las actividades.

Requisitos:

- 1- Niños que padezcan de 6 o más episodios asmáticos al año, que requieran medicamentos diarios o vacunación semanal para estar libre de síntomas.
- 2- Niños de ambos sexos entre las edades de 8-12 años (no haber cumplido los 13).
- Complementar la forma de solicitud en o antes de la fecha límite.
- 4- La participación de por lo menos uno de los padres o encargados en una actividad educativa y de orientación.

Dale la oportunidad a tu niño de vivir unas experiencias inolvidables que no sólo le servirán para recrearse sino para mejorar su salud física y mental. Para mayor información, comunícate con la Asociación Puertorriqueña del Pulmón más cercana:



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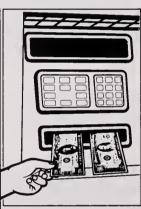
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ARTICULOS ESPECIALES

El Síndrome de Inmunodeficiencia Adquirida: Guías para el Control de Infecciones en el Paciente Ambulatorio y el Paciente Hospitalizado

Carlos H. Ramírez-Ronda, M.D., F.A.C.P.

Resumen: Estamos presentando una serie de medidas que se pueden utilizar para el control de infección del paciente tanto hospitalizado como ambulatorio con el Síndrome de Inmunodeficiencia Adquirida (SIDA). Específicamente se menciona la manera y las precauciones que debe tener el personal médico y paramédico en el hospital, el personal fuera del hospital así como las personas que bregan con los cadáveres y funerarios; se definen las guías a seguir por los dentistas que bregan con estos pacientes y se mencionan las precauciones que se deben tomar en cada uno de los procedimientos intrahospitalarios a los que se somenten estos pacientes y así evitar la transmisión de infecciones.

ElSíndrome de Inmunodeficiencia Adquirida (SIDA) (SIDA) ha tenido un despliege máximo en los medios de comunicación, tanto en Puerto Rico como en el resto del mundo y se encuentra entre un número de nuevas enfermedades para las cuales los especialistas en enfermedades infecciosas han sido consultados en la última década. Contrario a la enfermedad de los legionarios, que es causada por un bacilo gram-negativo, la artritis de Lyme, que es producida por una espiroqueta y el síndrome de shock tóxico, del cual una toxina estafilocócica es responsable, la etiología del Síndrome de Inmunodeficiencia Adquirida (SIDA) es desconocida. El agente etiológico más probable en este caso es un retrovirus conocido como HTLV-III.44

Para el invierno de 1985, un total de cerca de 7,000 personas tenían los criterios para definir SIDA y habían sido reportados en 41 de los estados, Puerto Rico y el Distrito de Columbia. 62, 64, 65 En otros países del mundo, específicamente en más de 20 países, se han identificado pacientes con SIDA.^{1, 2} Estudios preliminares revelan más de 500 casos en el continente americano, 600 en Europa y varios miles en Africa Central. 63 Cuando la mortalidad de esta condición se ajusta al año del diagnóstico, ésta se acerca a 100% en los primeros tres años después del diagnóstico.16 En Puerto Rico se han documentado 130 casos hasta diciembre de 1984, con una mortalidad de 57% y se están estudiando en la Clínica SIDA del Centro Latinoamericano para Enfermedades de Transmisión Sexual cerca de 150 pacientes en los cuales el diagnóstico se sospecha. 10 SIDA, aparentemente es transmitido por contacto sexual íntimo o por inoculación de sangre o productos de sangre. No hay evidencia de transmisión por contactos casuales o a través de contacto por el aire, ni se ha documentado que una persona adquiera SIDA trabajando en un laboratorio o proveyendo cuidado médico⁵, ²⁶ a pesar de que sí se reportó un caso de una persona que se pinchó con una aguja de un paciente que tenía SIDA y subsiguientemente se demostró que tenía una conversión serológica para el virus HTLV-III.

La transmisión es por contacto sexual o exposición parenteral en sangre.^{33, 51} Si se pueden detectar los porteadores del virus por pruebas serológicas, se puede disminuir significativamente la transmisión por sangre, sin embargo, la incidencia de SIDA transmitido por contacto sexual no se afectará hasta que se encuentre una vacuna o se tenga tratamiento para SIDA.⁴⁶ El virus HTLV-III se ha cultivado de linfocitos, nódulos linfáticos, semen y saliva de los pacientes con SIDA.⁹ Se pueden detectar anticuerpos en contra del virus en más del 90% de estos pacientes y en menos del 1% de individuos saludables.^{6, 67} El virus puede transmitirse verti-

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calmente de madre a feto.33, 51

La transmisión homosexual entre varones es responsable del 73% de los casos de SIDA en los Estados Unidos de América, la transmisión heterosexual ocurre pero con una frecuencia más baja, 5%, y es por contacto sexual con adictos en drogas, varones bisexuales y rara vez hemofilicos. La transmisión de mujer a varón no se ha documentado hasta enero de 1985 en E.E.U.U. a pesar de que 17/65 (26%) de varones que niegan pertenecer a algún grupo de riesgo admitieron contactos con prostitutas 4 y uno de los 17 había tenido más de 100 parejas sexuales en los últimos 5 años. Este patrón de promiscuidad heterosexual parecer ser el modo de transmisión de SIDA en Africa Central. La contral. La co

El diagnóstico de SIDA excluye las pruebas de laboratorio y depende de que aparezcan ciertas infecciones o neoplasmas que son poco usuales en la población en la cual están ocurriendo.29 Se excluyen pacientes de más de 60 años de edad, aquellos que están recibiendo tratamiento inmunosupresivo y pacientes que tengan enfermedades existentes asociadas a inmunodeficiencias. 59 Aproximadamente el 70% de los pacientes con SIDA son homosexuales o bisexuales varones, 17% son adictos a drogas endovenosas, 5% son haitianos, 1% son hemofilico y un grupo pequeño de pacientes, menos del 1%, han adquirido la enfermedad de transfusiones de sangre. Entre el 5 al 6% de los pacientes no pertenecen a algún grupo de riesgo ni han recibido transfusiones de sangre.⁵⁰ A pesar de que han ocurrido casos en niños nacido de madres con SIDA, estos niños se consideran aparte en la evaluación de los datos nacionales.³⁹

Aproximadamente el 50% de los individuos con SIDA se presentan con pulmonía por *Pneumocystis carinii*, 25% con el Sarcoma de Kaposi y el 7% tienen ambos. ¹⁶ El 16% se presentan con otras infecciones oportunistas tales como candidiasis mucocutánea crónica, Herpes simplex cutáneo, crónico y progresivo, enfermedad por *Mycobacterium avium-intracellulare* diseminada, meningitis criptocócica y meningitis causada por toxoplasma.

Los varones homosexuales y bisexuales están a riesgo de otras infecciones que son aún mucho más prevalentes que SIDA que incluye gonorrea, sífilis, hepatitis A y B, herpes anorectal, amebiasis, giardiasis, shigelosis, fiebre tifoidea, proctitis y uretritis por clamidia.^{8, 40} A pesar de que estas infecciones no causan SIDA, este tipo de infección aumenta colectivamente el problema del control de infección en estos pacientes.

Cualquier condición que no responda a tratamiento, que sea progresiva y sea causada por candida o por una infección de herpes por un período de 4 a 6 semanas de duración, a la misma vez que cualquier envolvimiento inesperado de un órgano, debe despertar la sospecha de SIDA en una persona que pertenezca a los grupos de alto riesgo. A pesar de que el diagnóstico de SIDA es clínico, se ha obtenido un número de datos de laboratorio. Casi todos los pacientes con SIDA, sin excepción, manifiestan linfopenia absoluta con una inversión de la razón de células T ayudantes a célula T supresoras. 16, 18, 21, 31 Debido a que se ha encontrado que cambios similares en esta razón están asociados a infecciones comunes como la hepatitis B, influenza, mononucleosis infecciosa, gonorrea, sífilis y linfoma, simplemente una prueba en la cual se

demuestra una disminución en la razón de células T ayudantes a supresoras, no puede ser considerada como diagnóstico de SIDA.³¹

Inicialmente se llevó a cabo una serie de estudios serológicos múltiples para definir el agente etiológico de SIDA o para establecer el diagnóstico. Se encontró evidencia serológica de una serie de infecciones que son indígenas en los grupos a riesgo y susceptibles a SIDA como son las infecciones por citomegalovirus, infecciones por el virus de herpes simplex e infecciones por el virus de hepatitis B. Se determinó que este tipo de asociación era más una asociación casual que la causa de SIDA. 18, 24, 47

A pesar de que inicialmente se pensó que era normal la proliferación de las células B, aparentemente no es selectiva, resultando en títulos altos de anticuerpos en contra de los agentes a los cuales estos pacientes han sido previamente expuestos y que son inmunes al momento de hacerse la prueba.^{24, 32, 56} Al mismo tiempo el paciente con SIDA falla al responder específicamente a nuevos antígenos y despliega respuestas anamnésticas de IgM, linfadenopatía angioinmunoblástica, y la proliferación de linfoma del tipo B.^{16, 32}

Comunicabilidad de las Infecciones en el Paciente con SIDA y Guías para Control

Pneumocystis carinii.

El 82% de los pacientes con SIDA se presentan con pulmonía por *Pneumocystis carinni* y/o el sarcoma de Kaposi. Las pulmonías por P. carinii se deben más probablemente a una reactivación endógena.²⁷ Sin embargo, debido a que ocurren brotes en pacientes inmunocomprometidos en salas pediátricas48, 53 puede asumirse razonablemente que los pacientes que tienen pulmonía por P. carinii deben de mantenerse con precauciones de mascarillas cuando están en los pasillos del hospital o pasando períodos largos en los departamentos de radiología. A pesar de que los casos de asociados a brotes sugieren transmisión entre personas, incluyendo el personal del hospital, algunos autores no creen que los datos hasta el momento dicten la necesidad de establecer aislamiento respiratorio para los pacientes con SIDA con pulmonía por P. carinii.48

Sarcoma de Kaposi.

El sarcoma de Kaposi es endémico en partes de Africa y se ha asociado con infecciones por citomegalovirus, 66 sin embargo, no hay evidencia que la presencia de este tumor conlleve a que se establezcan procedimientos específicos de aislamiento.

Micobacteriosis.

Los pacientes con SIDA pueden desarrollar infecciones micobacterianas e infecciones sistémicas por hongos.^{22, 23, 34, 37, 52, 54, 70} La enfermedad micobacteriana más frecuente que se encuentra es aquella causada por las cepas de micobacterias no tuberculosas, específicamente *Mycobacterium avium-intracellulare*, la cual no es transmisible de persona a persona.^{23, 34, 70} La identificación de un microorganismo en específico depende del laboratorio y puede tomar de 4 a 8 semanas. Por lo tanto, hasta

que se identifique definitivamente el microorganismo, aquellos individuos que son positivos en una tinción ácido resistente en un frotis de esputo, debe de aislarse inicialmente de acuerdo a las guías establecidas para el aislamiento de los pacientes que tienen tuberculosis causada por *Mycobacterium tuberculosis hominis*. Al mismo tiempo, se recomienda que el tratamiento inicial sea dirigido al grupo de *Mycobacterium aviumintracellulare*, que desafortunadamente, es mucho más difícil de tratar.

Infecciones por Hongos.

No hay evidencia de transmisión de humano a humano para criptococosis, histoplasmosis o coccidioidomicosis. ¹⁹ Por lo tanto, el diagnóstico de estas condiciones no exige que se implementen medidas de aislamiento o de control específicas en estos pacientes. Para los pacientes que tienen enfermedades severas de la piel por hongos y/o candidiasis cutánea, se recomienda que se tomen las precauciones establecidas para el aislamiento de heridas en este grupo de pacientes. ²², ³⁷, ⁵²

Infecciones Virales.

Frecuentemente, las infecciones causadas por el virus de hepatitis B, citomegalovirus, el virus de Herpes Simplex y el virus de Epstein Barr, han sido problemas crónicos en los dos grupos con más alto riesgo para desarrollar SIDA.^{37, 52} Deben de tomarse precauciones establecidas para el control de infección de Hepatitis B cuando se brega con sangre y/o secreciones en los pacientes con hepatitis B o sospechosos de hepatitis B hasta que las pruebas serológicas demuestren lo contrario.^{8, 40, 66} En el paciente con SIDA las precauciones arriba mencionadas están indicadas, irrespectivo del estado de la serología de hepatitis B, porque la epidemiología de SIDA sigue muy de cerca de la hepatitis B.³

EL citomegalovirus, fue el agente que se sospechó tempranamente ser el agente causante de SIDA; sin embargo, ahora se conoce que hay la misma prevalencia de este virus en pacientes con SIDA como en otros miembros de los mismos de grupos de riesgos que no tienen SIDA.¹³ Los pacientes con SIDA se pueden presentar con corioretinitis causada por citomegalovirus con una presentación única y aislada y pueden excretar el virus en la orina¹⁶ lo cual hace sospechar la posible transmisión a otras personas. El virus de citomegalovirus se ha encontrado en las adrenales de los pacientes con SIDA que mueren y se asocia con una manifestación de la enfermedad de Adison;57 esta es otra forma para el personal médico exponerse a un virus sin conocer que el paciente está infectado. Sin embargo, estudios en guarderías sugieren que las enfermeras no están a un riesgo más alto de adquirir citomegalovirus de casos en los cuales la infección congénita no se sospecha.

El paciente con SIDA también desarrolla lesiones cutáneas crónicas y persistentes causadas por el virus de herpes simplex que demanda que se tomen las precauciones establecidas para el aislamiento de heridas. Es la opinión de varios autores que la mujer embarazada debe de evitar contacto directo con pacientes con SIDA.¹⁹

Patógenos Gastrointestinales.

Los patógenos que se recobran de la excreta de los pacientes con SIDA ofrecen el riesgo más alto de infección y transmisión intrahospitalaria de enfermedad al personal médico o a otros pacientes. El síndrome gastrointestinal de los homosexuales se ha descrito en varones homosexuales sin SIDA en los cuales han ocurrido brotes o casos individuales de salmonellosis aguda a crónica, shigellosis, campylobacteriosis, amebiasis, giardiasis, y yersiniosis.^{8, 41} Si en un cultivo se recobra cualquiera de los agentes etiológicos arriba mencionados, con la excepción de salmonella, es una indicación para tratamiento específico basado en la identificación de este microorganismo. No está claro si los pacientes con SIDA que solamente tienen un cultivo positivo para salmonella y que probablemente están a un riesgo mayor para invasión sistémica deben de recibir tratamiento antimicrobiano. Obviamente, la salmonellosis asociada a manifestaciones sistémicas debe de tratarse.68

Criptosporidium es un nuevo agente etiológico de diarrea en pacientes con SIDA. Este protozoario se ha asociado con diarrea crónica persistente, que no cede y que termina en malnutrición, pérdida de peso y muerte. 55 Previamente se consideraba que este organismo no afectaba los humanos causando diarrea en el ganado vacuno, con reportes ocasionales de enfermedad autolimitante que se veía en pacientes que la adquirían por su tipo de trabajo. "Spiramycin", un antibiótico macrólido, está disponible para el tratamiento de esta condición en el Centro de Enfermedades en Atlanta, Ga., y es el mejor agente terapeútico que se conoce, aunque no es tan efectivo. 61

El Paciente con Diarrea.

Todos los pacientes hospitalizados con fiebre y diarrea deben de ponerse en precauciones para heces hasta que se documente la evaluación microbiológica. Algunos autores creen que todos los pacientes con SIDA sin queja de diarrea o fiebre pero que tienen problemas con la higiene personal ya sea por sus problemas neurológicos, debilidad, o incontinencia deben de ser puestos en precauciones para heces hasta que se tengan cultivos negativos. Esta acción está indicada debido al potencial de colonización asintomática con transmisión subsiguiente al personal del hospital y a otros pacientes (Véase Tabla I)

Como Manejar el Paciente con SIDA: Guías para Evitar Posible Contagio

Los pacientes con SIDA, también como aquellos pacientes que tienen el sarcoma de Kaposi y que son menores de 60 años, y los pacientes con linfadenopatía crónica, pérdida de peso, y/o fiebre prolongada "el complejo relacionado a SIDA", los cuales admiten pertenecer a los grupos de alto riesgo para SIDA, son vistos con frecuencia para cuidado médico tanto en forma ambulatoria como en forma intrahospitalaria. Debido a que con frecuencia estos pacientes son donantes de sangre, tienen numerosas pruebas serológicas diagnósticas, son sometidos a procedimientos diagnósticos como endoscopía y requieren trabajo dental, el control de

Tabla I

Enfermedad	Cuarto Privado	Bata	Mascarilla	Guantes	Material Infeccioso	Duración de Precauciones
SIDA	Si la higiene es pobre	Si es probable ensuciarse	Sí succión vigorosa, endoscopías	Para tocar material infeccioso	Sangre y/o secreciones	Toda la enfermedad
Pulmonía por Pneumocystis carinii	No	No	?	No	-	-
Sarcoma de Kaposi	No	No	No	No	-	-
Cryptosporioidosis	Si la higiene es pobre	Si es probable ensuciarse	No	Para tocar material infeccioso	Heces	Toda la enfermedad
Infección por CMV	No	No	No	No	Orina y Secreciones Respiratorias	-
Toxoplasmosis	No	No	No	No	-	-
Mycobacterium avium- intracellulare pulmonar	No	No	No	No	-	-
Herida	No	Si es probable ensuciarse	No	Para tocar material infeccioso	Sangre y/o secreciones	Toda la enfermedad

infección en este grupo y guías para disminuir el riesgo de contagio es pertinente para todas aquellas personas que proveen cuidado médico a la misma vez que para todas aquellas personas que trabajan en el laboratorio y que pueden estar expuestas a los tejidos, a las secreciones y/o sangre de este grupo de pacientes. También, la alta mortalidad asociada con SIDA ha generado que se establezcan guías para el control de infección para aquellas personas que llevan a cabo necropsias y/o que proveen servicios funerarios.¹⁴

Precauciones Generales.

Una de las precauciones que se pueden tomar en la comunidad, individualmente y colectivamente, es evitar el contacto sexual o el contacto con jeringuillas de pacientes que se conozca que tengan SIDA o que pertenezcan a los grupos que están a alto riesgo de SIDA.^{7, 45} Los miembros de los grupos de alto riesgo deben estar conscientes que el uso endovenoso de drogas y que los parejos sexuales múltiples aumentan el riesgo de desarrollar SIDA. Es la opinión de varios autores que no es necesario cuartos de exámenes separados en áreas de pacientes ambulatorios, ni que los pacientes con SIDA se les requiera esperar en áreas separadas o tener facilidades de baño separados.¹¹

La Sangre y sus Productos como Vehículos de SIDA: Donantes de Sangre, Guías para Control

Aunque raro, SIDA ha ocurrido en pacientes que han recibido productos sanguíneos al azar. 12, 30 Aparente-

mente, hay un riesgo aún más alto en los pacientes hemofilicos que reciben el factor 8 concentrado liofilizado. 15, 60 La Cruz Roja Americana, la Asociación de Bancos de Sangre Americana y el Consejo de Bancos de Sangre de la Comunidad han recomendado el que no se utilicen donaciones directas. 49 El riesgo bajo de SIDA no debe ser un factor que prevenga que una persona muera debido a que le falte sangre o productos de sangre. Hasta el momento, estas organizaciones han recomendado que todo paciente que tenga SIDA o que pertenezca a los grupos de alto riesgo de SIDA no se acepte o se evite que sea un donante de sangre. 45

Como siempre, los proveedores de cuidado médico deben de estar seguros que los productos de sangre se usen apropiadamente. Se tiene esperanza que con la identificación del agente etiológico de SIDA, se puedan desarrollar pruebas serológicas que permitan cernir a los donantes de sangre y no aceptar aquellos que sean positivo. Sin embargo, la implementación de este tipo de prueba tiene que tomar en cuenta la especificidad de ésta y la interpretación de una serología positiva no necesariamente conlleva a un diagnóstico. El impacto de esta prueba en el suplido de sangre y selección de donantes debe de estudiarse. La implementación de esta prueba debe de tener en conciencia mantener la privacidad de los donantes.35 Basándose en la falta de especificidad y costo de las razones de células T ayudantes a supresoras, ésta no es una prueba práctica para cernimiento. El desarrollo de sangre sintética también eliminaría el riesgo de complicaciones infecciosas.

Los historiales en el momento en que se acepta un donante o en el momento que se admite un paciente deben de ser refinados para sacar los datos que puedan sugerir que el paciente pueda estar a riesgo de SIDA. A los donantes debe de dársele la opción de telefonear al sitio en donde donaron la sangre para que pidan o puedan pedir que su sangre no se use para transfusiones humanas. Esto permite que un individuo pueda participar en una actividad de su lugar de trabajo o club en donde se recolecciona sangre sin estar marcado por el grupo, pero a la misma vez puede estar consciente de su condición y llamar para que su sangre no sea utilizada.

Procedimientos de Control en el Hospital.

En algunas instituciones el paciente hospitalizado con SIDA se maneja con las mismas precauciones que se tiene con un paciente hospitalizado con el virus de hepatitis B.41, 45 Hasta enero de 1985 no había una prueba comercial que pudiese identificar aquellos pacientes que puedan transmitir SIDA a otras personas. En febrero o marzo de 1985 comenzará a estar disponible una prueba comercial utilizando el método de ELISA para cenir los donantes de sangre, su aplicación como marcador de infectividad y comunicabilidad se desconoce hasta el momento. Hasta que se tengan otros datos, la política de manejar estos pacientes como los que tienen hepatitis B debe de continuarse mientras el paciente esté hospitalizado. Es indispensable tomar precauciones con la sangre y las secreciones del cuerpo de estos pacientes. Las muestras deben de ser marcadas apropiadamente en una bolsa doble o en un recipiente sellado que haya sido contejado para roturas y utilizar sólamente este tipo de envases.30

Como la confidencialidad del paciente ha generado una serie de preocupaciones sobre el uso del nombre SIDA,14 algunos autores han sugerido utilizar un marcador genérico para todas las enfermedades que requieren precauciones con la sangre y las secreciones del cuerpo. Simplemente, si se pueden marcar estas muestras con el nombre "hepatitis B" o "precauciones de hepatitis B" esto puede llenar el cometido y la meta, pero también puede dar lugar a que se lleven a cabo pruebas diagnósticas y terapeúticas si por una casualidad ocurre una exposición ya sea de una mucosa a través de un pinchazo de aguja. Se debe evitar también que individuos que son inmunes a hepatitis B tengan un falso sentido de seguridad. En muchos hospitales se usan los marcadores que dicen "precauciones para sangre y líquidos del cuerpo". Otros han utilizado una codificación a color o un emblema para que indique que hay un peligro biológico. Las agujas que se usan en los pacientes con SIDA deben de ser desechables y no deben de volverse a tapar.^{36, 69} Debe de utilizarse una unidad sellada o una aguja del tipo con cierre para evitar que ocurra salida de la sangre y contaminación de la persona que sangre al paciente.

Un procedimiento muy importante es el procedimiento de una buena técnica de lavado de mano que debe de seguirse antes y después de cada visita al paciente y deben de utilizarse guantes cuando se anticipa exposición a sangre o exposición a las secreciones del cuerpo del pacientes. 11, 55 Si se anticipa que pueda ocurrir conta-

minación de la ropa entonces deben de utilizarse las batas desechables, específicamente si puede ocurrir contaminación con sècreciones, excreciones, líquidos del cuerpo y/o contaminación con sangre. Deben de utilizarse máscarillas cuando se lleva a cabo una succión vigorosa o cuando el paciente tiene enfermedades que se pueden transmitir a través del aire como la tuberculosis humana. Los cuartos privados no son mandatorios mientras el paciente no esté tosiendo y pueda mantener su higiene personal; sin embargo, los pacientes con SIDA prefieren este tipo de cuarto. El uso de cuartos privados también evita las situaciones desagradables que resultan de la ignorancia del público. 11 Se debe disponer de los agentes desechables que se usan en el cuidado rutinario del paciente en la forma usual; sin embargo, si estuviesen cubiertos con sangre o con secreciones del cuerpo, deben de ser tratados como si fuera material infeccioso. Aquellos objetos que son reusables deben ser tratados como si el paciente tuviera hepatitis B. Los pacientes que requieren diálisis peritoneal o hemodiálisis deben de maneiarse igual que un paciente conocido con hepatitis B activa. 49 En este momento es prudente que los pacientes que tengan SIDA no donen sus órganos.

Precauciones en el Laboratorio.

En el procesamiento en los laboratorios de la sangre y las secreciones deben de utilizarse las precauciones establecidas para hepatitis B.3, 14, 17 Específicamente, toda persona que trabaja en el laboratorio debe de utilizar batas y quitárselas antes de salir del trabajo. Se deben utilizar guantes para evitar contacto de la piel con muestras de los pacientes con SIDA. Se deben tomar precauciones para evitar pinchazos con agujas. No se debe y no se puede pipetear con la boca. Las superficies contaminadas con sangre o secreciones del cuerpo deben de ser lavadas con una preparación de hipoclorito de sodio al 5.25% diluído de 1:10 con agua. Todos los productos, tanto los desechables como los reusables, deben de ser autoclaveados antes de disponer de ellos. A pesar de que no hay evidencia de que SIDA se transmite a través del aire o a través de pequeñas partículas, es razonable tratar de evitar su creación, la cual podría resultar en la exposición de las membranas mucosas. El potencial para esta exposición es la más alta cuando se están trabajando con sorteadores celulares; debe de utilizarse un sistema de seguridad biológica, si está disponible, cuando se brega con estas muestras.

Precauciones en el Laboratorio Experimental.

Para aquellos que bregan con animales experimentales, las precauciones son iguales a las del personal de laboratorio.³, ¹⁴, ¹⁷ Estas personas deben de utilizar batas, guantes y sobre-espejuelos porque los animales muchas veces muerden y botan excremento. Las jaulas deben de ser autoclaveadas, si posible, y luego desinfectar utilizando el hipoclorito de sodio como antes se describió.

Precauciones para el Laboratorio de Patología y Funerarias.

Los patólogos y las personas que bregan con cadáveres en funerarias que bregan con muestras en las cuales se sospecha SIDA deben de seguir las precauciones que se sugieren para aquellas muestras con hepatitis B.⁴, ¹⁴ Los tejidos deben de ser fijados en 10% de formalina antes de ser cortados. En la autopsia, las personas que trabajan deben utilizar guantes dobles, mascarillas, sobreespejuelos, delantales y cubiertas para sus zapatos a prueba de agua. Los instrumentos que están potencialmente infectados deben de ser autoclaveados antes de ser reusados; las superficies deben de ser descontaminadas con hipoclorito de sodio. Las personas que bregan en la funeraria deben de seguir las mismas recomendaciones que se le hacen a los patólogos.

Precauciones para los Dentistas.

Los dentistas que tratan pacientes con SIDA deben de utilizar guantes, máscarillas y sobre-espejuelos para prevenir la exposición de sus membranas mucosas.

Precauciones para los Endoscopistas.

Los endoscopistas deben de utilizar guantes, mascarillas y sobre-espejuelos para evitar que ocurra exposición orofaringeal o de conjuntiva cuando examinan estos pacientes. 38 Los endoscopios deben de ser esterilizados con gas antes de ser reutilizados y todas las partes desechables descartadas de acuerdo a la política establecida para manejar material infeccioso. Muchos autores recomiendan a los endoscopistas que lleven a cabo los procedimientos no urgentes en los pacientes con SIDA al final del día de tal manera de que en el momento en el que hay muchos pacientes, esto no dé lugar a que las medidas de esterilización y de mantenimiento del lugar no se lleven a cabo propiamente. Estas guías también se aplican a los broncoscopios, esofagoscopios, gastroscopios, colonoscopios y cistoscopios.

Otros Posibles Areas de Precaución.

El uso de ventilación artificial en el paciente con SIDA establece una serie de preguntas únicas para las cuales no se tiene una contestación específica. Idealmente, el aire debe ser ventilado hacia afuera. Algunos autores han recomendado que se utilize una sola enfermera en cada cuarto y que esta enfermera mientras esté en ese cuarto utilize batas, guantes, mascarillas y sobre-espejuelos.³⁸ Como no hay evidencia de transmisión a través del aire, aún en personas que viven en las casas con los pacientes con SIDA, algunos autores creen que estas recomendaciones son exageradas. Ciertamente, si se conoce que una enfermedad respiratoria que se puede comunicar está presente, se debe de tomar precauciones. Además, cuando se succiona a uno de estos pacientes, es indispensable utilizar máscarillas y sobre-espejuelos. Cuando se lleva a cabo espirometría se debe de utilizar el equipo desechable. El espirómetro debe de ser ventilado con aire del cuarto varias veces para estar seguro de que sus tubos se han limpiado de todas las secreciones antes de que vaya a ser reutilizado en otro paciente. Las bolsas de resuscitación o los instrumentos de resuscitación cardiopulmonar desechables deben de mantenerse al lado del paciente.

Visitas al Paciente con SIDA.

No hay alguna política de control de infección y de procedimiento para las personas que visitan al paciente con SIDA a menos que se conozca específicamente que éste tiene una enfermedad contagiosa definida como sería salmonellosis o tuberculosis. Si hay exposición a la sangre o a las secreciones del cuerpo del paciente, se deben tomar las precauciones establecidas para los empleados del hospital. Las personas que visitan el hospital y que están enfermas, lo mismo que a los empleados enfermos, no se les debe permitir que tengan contacto con los pacientes con SIDA, los cuales están usualmente severamente enfermos mientras están en el hospital y tienen una disminución marcada de sus defensas.

El Empleado con SIDA y Responsabilidad del Empleado.

A los empleados asintomáticos que tengan SIDA puede permitírseles continuar trabajando, ^{8, 14} pero no en una capacidad en la cual su sangre o secreciones del cuerpo puedan tener contacto con pacientes. La presencia de una enfermedad contagiosa con una prohibición específica de salud pública para empleo requerirá restricciones en el trabajo hasta que el problema se resuelva. No es recomendable de que empleados que tengan malignidades, que estén recibiendo quimioterapia o que estén inmunocomprometidos o embarazadas, tengan contacto con pacientes con SIDA. Si un empleado abandona la responsabilidad y decide no proveer cuidado a un paciente con SIDA, éste es un problema moral, social, ético y legal en vez de un problema científico y debe de ser manejado de esa forma.

Vacuna de Hepatitis B y SIDA.

Recientemente, se han formulado una serie de preguntas sobre la seguridad de la vacuna de hepatitis B derivada del plasma porque el material fue obtenido de individuos que tenían hepatitis B crónica y que algunos de ellos eran miembros de los pacientes que están a alto riesgo de SIDA.²⁰ La purificación con ultracentifugación e inactivación con pepsina, urea y formalina hacen que sea muy poco probable que algún agente transmisible pueda sobrevivir.21 A pesar de que el HTLV-III específicamente no ha sido probado, otros retroviruses son destruidos por formalina. No hay casos reportados de pacientes que hayan desarrollado SIDA por asociación por la vacuna en personas fuera de los grupos de riesgo de SIDA.25, 58 Dentro de los grupos de alto riesgo, la frecuencia de SIDA ha sido similar en los individuos vacunados y en los no vacunados. Si miramos en términos generales y consideramos el riesgo y beneficio, el análisis sugiere que todas las personas que están a alto riesgo de hepatitis B se benefician cuando reciben la vacuna de hepatitis B.²⁵

El Futuro.

Se anticipa que una vez se identifique finalmente el agente etiológico de SIDA y que se desarrolle una prueba de cernimiento, esto nos ayudará grandemente en el diagnóstico y en el manejo de los pacientes que vemos diariamente; la implementación de la política de control

de infección y la política del control de los procedimientos igual que el problema del manejo de estos pacientes debido a las cargas sicológicas y emocionales se resolverán una vez se pueda identificar estos grupos. El futuro está muy cerca, pronto, en varios meses, tendremos una prueba para detectar la presencia de anticuerpos en contra de HTLV-III a base de ELISA. La pregunta que requerirá más datos para ser contestada es, qué significa positividad por ELISA en el diagnóstico y prognóstico del paciente asintomático. La prueba nos ayudará a excluir donantes con seropositividad, pero a la vez puede comprometer el suplido de sangre, si las personas que desean saber su estado serológico utilizan los bancos de sangre como una forma de obtener la prueba gratis. La confidencialidad de la prueba debe mantenerse ya que se puede utilizar para marcar y excluir grupos; una prueba de ELISA positiva debe de ser confirmada preferiblemente por la técnica de "western-blot". La implicación en la salud pública necesita estudio y las guías tienen que establecerse.35

Summary: A series of control measures is presented to serve as a guide in infection control of outpatients as well as inpatients with the Acquired Immunodeficiency Syndrome (AIDS). Specifically, we mention the way to handle patients with AIDS and the precautions that should be taken by the medical and paramedical personnel when dealing with these patients. Precautions for pathologists, morticians and dentists are also outlined. We discuss the guidelines that should be followed by the personnel to protect themselves and to sterilize the equipment utilized in invasive procedures. The goal is to educate medical and paramedical personnel as to the way to deal with the AIDS patient.

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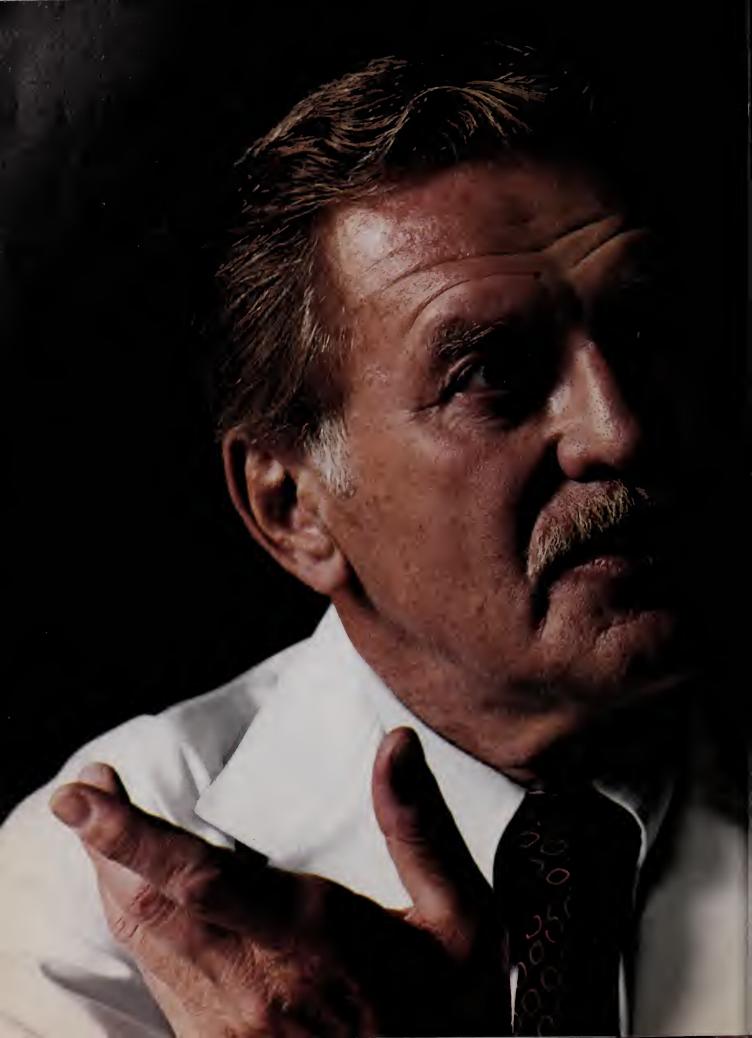


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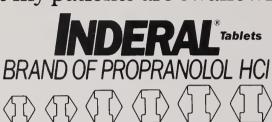
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the failure is secondary to a tachyarrhythmia treatable with INDERAL WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and duretics. Beta-adrenergic blocking agents do not abolish the inortopic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with duretics, and the response observed closely or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice if INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary atterty disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonalergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholarmine stimulation of beta receptors MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted. however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgicial procedures.

the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers. DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labite insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General Propranotol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients

90 mg*

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfer with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure. Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase. DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

which may result in hypotension, marked oracycardial, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility, Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was

age levels. Reproductive studies in a final sold hot show any inipalinient of leftility that was attributable to the drug. Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is excreted in human milk.

INDERAL is administered to a nursing woman Pediatric Use Safety and effectiveness in children have n ADVERSE REACTIONS ess in children have not been established

Most adverse effects have been mild and transient and have rarely required the withdrawal of

therapy Cardiovascular bradycardia; congestive heart failure, intensification of AV block, hypotesion, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the

Raynaud type
Central Nervous System. Lightheadedness, mental depression manifested by insomnia Central Nervous System. Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. Gastronitestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

*Allergic** pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

*Respiratory** bronchospasm

*Hematologies** agranulocytosis, popthrombocytopenic purpura, thrombocytopenic.

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic

purpura
Auto-Immune In extremely rare instances, systemic lupus erythematosus has been

reported Miscelfaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolal) have not been associated with propranolol *The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories

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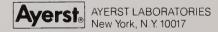




Fig. 2. Summed image, of the study, 15-30 seconds.

tion to the physician. discomfort to the patient and provides plenty of informarequisite is accesibility of a vein. It causes minor localizes possible occlusion of great vessels, its only about patency of veins, gives direction of flow, and tions. Isotopic phlebography reliably offers information graphy with probable release of small partial obstrucmechanism of injection-high pressure in contrast venoration and evaluation. He attributes this to the highly stereotyped procedure for venous system explowere not always delineated by contrast venography, a channel and collateral pathways. Ramesh found these uni or bilaterally. This gives a display of the major venous pertechnetate is injected in bolus along the femoral vein, accuracy. The radioactive material, 99m-Technetium efficacious, noninvasive procedure with high yield and nuclide images of the inferior vena cava, is a simple, The diagnostic test realized in this patient, radio-

Resumen: Se ilustra el uso de la angiografía radionuclear en el diagnóstico de obstrucción de la vena cava inferior causada por fibrosis retroperitoneal.

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tinguishable from lymphoma, sarcoma or metastatic disease.*

In this patient, many features of RF were found - a 67 Gallium scan realized 3 years prior to admission revealed increased localization relative to paraaortic nodes. Bilateral hydronephrosis with renal failure, insertion of ureteral catheters, diabetes de novo and hypertension which subsided spontaneously implied an infiltrative retroperitoneal process. Finally, a late congestive heart failure with dependent pedal and scrotal edema, external hemorrhoids and trophic changes in both lower limbs are manifestation of internal organ compression. This eventually led to the suspicion of a commonly found condition in this disease; inferior vena cava syndrome with thrombosis.

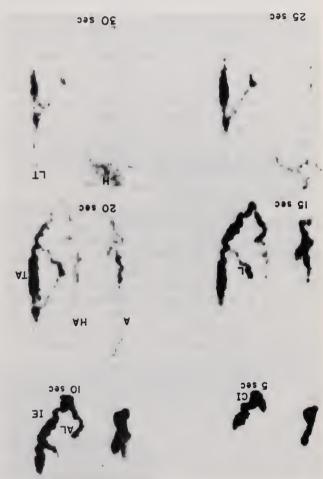


Fig. 1. Radionuclide angiogram (99mTc pertechnetate) following injection in both femoral veins demonstrates flow of the material into several deep and superficial collateral veins as follows: circumflex iliac (CI), ascending lumbar (AL), inferior epigastric (IE), lumbar (L), thoraco-abdominal (TA). The azygos (A) and hemiazygos (HA) and later the heart (H) were seen but no flow was demonstrated through the inferior wera cava. Collateral flow from inferior epigastric to thoraco-abdominal (TA) and lateral thouracic (LT) veins is also seen. Note tortuosity of some of these vessels.



Foro de Medicina Nuclear

(99mTc pertechnetate) Radionuclide Venography Inferior Vena Cava Obstruction: Retroperitoneal Fibrosis and

Julio V. Rivera, M.D. Luis Piñeiro Pérez, M.D. Estela Torres Irizarry, M.D.

of the inferior vena cava below renal level. azygos vein, thus demonstrating compressive obstruction to cross the midline to enter the inferior vena cava and cava. At the level of the kidneys, the bolus was observed lumbar vein, but no flow initially along the inferior vena material into superior epigastric and left ascending Radionuclide imaging revealed splitting of radioactive the radioactive material into the right femoral vein. Technetium pertechnetate was realized, after injection of On August 21, 1984 a scintigraphic venogram with 9m-

Discussion

traumatic and surgical events, may be primary causes. aortic aneurysm, collagen diseases, infectious processes, eventual RF. Other pathological conditions, such as described to cause some kind of vasculitis,1 causing hydralazine and methyldopa, and some others have been use of methysergide; certain cardiac drugs, such as retroperitoneal fibrosis (RF) has been associated to the 2:1 male-semale ratio. A suspected autoimmune disease, commonly in adults in their fourth to sixth decade, with a condition of uncertain etiology. It presents most scarry material in the retroperitoneum, is a pathological Retroperitoneal fibrosis, an infiltrative proliferation of

Advanced fibrosis may cause anuria and dysuria, with back and abdominal pain, and constitutional symptoms. Signs and symptoms include insidious onset of dull

renal involvement and hypertension.

Gallium scans performed in a patient with RF are indissonogram, give no pathognomonic landmarks.5 67 well as nuclear magnetic resonance and abdominal been reported by computed tomography, but these, as descriptive patterns of presentations radiologically have phrosis, and medial deviation of ureters.2 Different teristic triad of ureteral obstruction, proximal hydrone-The diagnosis by intravenous pyelogram is a charac-

Case Summary

every night. No pleuritic or retrosternal chest pain or referred paroxysmal nocturnal dyspnea, up to 2-3 times failure. Two weeks prior to admission, the patient admission, attributed at that time to congestive heart of lower limbs and genitalia since three months prior to inserted on March 19, 1984. He had progressive swelling and hypertension. Ureteral catheters were bilaterally fibrosis, diabetes, ureteral obstruction with hydronephrosis has a history of myocardial infarction, retroperitoneal Ltime because of bilateral leg swelling. The patient 56 years old white male was admitted for the sixth

edema of both lower limbs and trophic coarse leg changes There was a large external hemorrhoid, severe pitting shifting dullness was not detected. Liver span was 15cm. were observed. His abdomen was non-tympanitic and blowing murmur. Superficial collateral abdominal veins third heart sound (S3), and a faint mitral regurgitant is observed to have jugular venous distention at 45°, a At physical examination, a chronically ill male patient dyspnea on exertion were reported.

Initial diagnostic impression was congestive heart bilaterally.

inferior vena cava constriction was done. ischemic cardiomyopathy with low cardiac output and No pericardial effussion was observed. An assessment of and apex and an ejection fraction of approximately 30%. showed left atrial enlargement with dyskinetic septum the report of microscopic hematuria. An echocardiogram failure. Laboratory examinations were normal except for

of Medicine, San Juan, Puerto Rico of Medicine and Radiological Sciences, University of Puerto Rico School Administration Medical and Regional Office Center and the Departments From the Nuclear Medicine and Medicine Services Veterans

evaluating the efficacy of calcium antagonists in patients, preliminary reports on randomized trials drug of choice in coronary vasospasm. In post-infarction in combating exercise-induced ischemia and they are the Calcium antagonists: Calcium antagonists are effective

Nitrates: Data from prospective randomized studies negative to date.

the beta-blockers and are corner-stones in the treatment progress. These drugs have anti-ischaemic actions like and re-infarction are currently not available; trials are in concerning the efficacy of nitrates in preventing death

ventricular ectopy at the time of hospital discharge after Anti-arrhythmic drugs: Frequent and/or complex

MI are markers of high risk for sudden death in the

excluded through Holter-monitoring and/or electroarthythmic efficacy should be assured and adverse effects patients with serious ventricular arrhythmias, but antiarrhythmic treatment should be considered in individual on survival of specifically suppressing arrhythmias. Antionly one of these trials was designed to evaluate the effect interventions with anti-arrhythmic agents. However, Randomized studies have not shown benefit from

of angina pectoris.

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levels and even access to care.

20th century."

during the first

"He flourished

half of the

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he American physician isn't extinct. But your freedom to

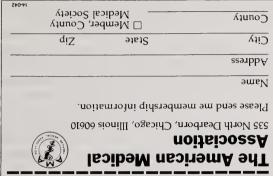
practice is endangered. Increasing government intervention

cost containment pressures from myriad sources, has taken a

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ensuing year.

preventing death and recurrent infarction have been



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or total mortality. reduction in myoçardial re-infarction but not in coronary coronary and total mortality; the second, a significant

combination with other drugs (e.g., beta-blockers) is prevention of CHD, including whether their use in drugs are needed to clarify their role in secondary Results from further studies with platelet-influencing

more effective than their administration alone.

Anticoagulants

pathogenesis of MI and in the post-infarction period. coagulation processes play an important role in the CHD is based on the available evidence indicating that The rationale for anticoagulation of patients with

indicated an increased risk of MI after discontinuation of anticoagulants long-term before entering the trial, patients above 60 years of age, who were on oral Findings of a Dutch randomized study of post-MI control groups; this latter difference in not significant. 13.1% in the anticoagulated groups and 19.3% in the Mortality due to cardiac causes in these studies was anticoagulated groups and 22.9% in the control groups. studies occurrence of re-infartion was 12.9% in the recurrent infarction in the treatment group. In these control groups, one finds a significant reduction of long-term oral anticoagulation and 2,256 patients in randomized trials evaluating 2,331 patients treated with Long-term anticoagulation: Pooling the data of 16

in patients with chronic cardiac failure, atrial fibrillation, available. Long-term anticoagulation may be mandatory acceptable, and if a reliable laboratory control is patients are carefully selected, if patient adherence is can be recommeded after myocardial infarction, if In summary, long-term anticoagulation with coumarins

and/or left ventricular aneurysm.

nitrates and anti-arrhythmics revascularisation, calcium antagonists, Continuing ischemia after MI:

global left ventricular function. angina patients with multi-vessel disease and impaired superior to medical management in chronic exertional surgical and medical management. Surgical results are mortality or re-infarction rate long-term between only mildly symptomatic, there is no difference in angina and in post-MI patients who are asymptomatic or United States showed that, in CHD patients with mild However, the recently completed CASS trial in the patients with post-infarction angina treated surgically. recently reported a 10 year survival of 83% in over 400 randomized studies are not yet available, one center has very high mortality. Although surgical results from that medical management in this high risk group carries a cularisation. This recommendation is based on the fact out in these patients with a view toward possible revasit is recommended that coronary arteriography be carried with a high risk of mortality within the first year, Hence, after recovery from the immediate infarction is associated tion angina, or ECG or other test evidence of ischaemia) Revascularisation: Continuing ischaemia (post-infarc-

> There is also evidence that some beta-blockers given in particular drug, on dose level, or on choice of patients. positive findings and benefit may depend on the before hospital discharge. Not all trials have yielded treating them. If used, beta-blockers should be started further 25% reduction would not justify the trouble of blockade, unless their absolute risk is so low that even a

blockers has any salutary effects on late outcome. has not been established to date that the early use of betathe acute stage of MI may reduce infarct size. However, it

Platelet function inhibiting drugs

be established. for the possible prevention of vascular occlusion is yet to sial. An optimal daily dose of acetylsalicylic acid (ASA) be inhibited by antithrombotic agents remains controverfunctions. The question which platelet functions should obtained. Available drugs inhibit different platelet gation. Promising but not conclusive results have been undergone bypass surgery is still under active investimyocardial infarction and in patients who have The use of platelet function inhibitors in survivors of

of reinfarction. have a significant beneficial effect in reducing incidence first year of daily ASA treatment. ASA was also found to beneficial trend was particularly pronounced during the combined ASA reduced total mortality by 10%. This largest trial was negative, based on all the studies results of these trials were not entirely consistent and the patients have been published and reviewed. While the triasl of ASA involving over 11,000 post-infarction Data from 7 randomized placebo-controlled clinical

reduced by 51%. group, death and myocardial infarction were significantly in 1,266 patients with unstable angina. In the treatment with a dosage of 324 mg/day was compared with placebo In a recently published study 12 week's ASA treatment

.ASA + əlomsbiryqib from MI is currently being tested in a second trial of efficacious particularly for patients recently recovered ASA alone. The possibility that active medication was tion of dipyridamole + ASA was more effective than study did not yield clear-cut evidence that the combinaof 16% to 25%— were not statistically significant. The causes mortality. These favourable trends —in the order fatal MI plus fatal CHD, coronary mortality, and all similar reductions were recorded in incidence of nonpatients recovered from MI. For both active treatments, + ASA and ASA alone were compared with placebo for In the dipyridamole-ASA re-infarction study, dipyridamole

occlusions in the treated group. 12 months there was a significant reduction in graft coronary bypass surgery. After one month and also after compared with placebo in patients who underwent In another study, ASA and dipyridamole were

anticipated when this drug is prescribed for long-term the potential adverse effects of ASA that need to be occasional massive gastro-intestinal bleeding are among Gastric distress, minor blood loss in the stool, and

completed. The first, reported a marginal reduction in Two controlled trials with sulfinpyrazone have been

a fall in high density lipoprotein levels. glucose tolerance, and —depending on their composition increase in serum triglyceride levels, and a reduction in tend to induce a rise in blood pressure and weight, an certain physiological and metabolic processes. Thus, they established that they significantly and adversely alter contraception in industrialized society. It is now well

atherosclerotic arteries. vulnerable blood vessels, such as varicose veins and ficant thrombogenesis is more likely to occur in beyond age 35 years, and by cigarette smoking. Signichanges are aggravated with increasing age, particularly fibrinolysis, and platelet function. These thrombogenic vascular endothelium and alter blood coagulability, Oral contraceptives also affect the integrity of the

cholesterol. and who have a normal blood pressure and plasma venous disease, pulmonary embolism, or arterial disease, who do not smoke, who do not have a previous history of Oral contraceptives are safe in women under 35 years

irrespective of age. a history of thromboembolic or atherosclerotic disease, hypertension, frank hypercholesterolaemia, diabetes, or advised to avoid the pill, as should smokers, women with episode. In general women over 35 years should be to report any symptoms which suggest a thrombotic blood pressure and weight checks, and should be advised Patients on oral contraceptives should have regular

tions are not observed. the risks are not negligible if the aforementioned precauare safer than those with higher doses, but nevertheless Oral contraceptives containing a low dose of oestrogen

postmenopausal women Oestrogen therapy in menopausal and

has not been established. in menopausal and postmenopausal women with CHD The risk/benefit ratio of long-term oestrogen therapy

Vasectomy

the physician. vasectomy must be left to the discretion of the patient and indicated in coronary patients. A decision about evidence that the procedure is either indicated or contraand atheroselerosis in non-human primates, there is no Despite a report of an association between vasectomy

Drugs and Surgery for Secondary Prevention

Beta-blockers

majority of patients after MI gain from prolonged betaindications are avoided, the trial results suggest that a were present or not. As long as patients with clear contrations to beta-blockers, regardless of whether symptoms performed in patients who had no major contraindicareinfarction was also observed. These trials were was reduced by 26% to 39% and a reduction of nonfatal ment was started prior to hospital discharge. Mortality Norway, Sweden, and the USA. In these studies, treatmyocardial infarction were recently reported from Three positive trials in a large number of patients after

> times weekly, at 70% of the highest heart rate achieved at to 45 minutes duration, repeated at least two to three The training effect can result from active sessions of 30

physical exercise testing (where available).

All physical training programmes should initially be time (such as walking) can benefit physical performance. impaired patients, low level activity for longer periods of improve physical fitness. In older and physically more Even shorter periods of exercise (15 to 20 minutes) may

deleterious effects on the heart, but did improve physical ventricular function did not result in beneficial or exercise in patients with slight to moderate impairment of up. There is evidence that appropriately prescribed done under medical prescription and should be followed

function, physical exercise may be beneficial, but requires Even in patients with severe impairment of ventricular pertormance.

careful dosage guidance and overall control.

Patients who receive beta-blocking substances can also

be trained.

Psychosocial stress

sudden death, in coronary patients. life stresses can precipitate recurrent events, including research data from a few studies — indicates that acute Extensive clinical experience — supported by recent

prevention. by the patients to recommendations for secondary tion between patient and physician, and good adherence, major obstacles standing in the way of effective coopera-Negative life events and psychosocial stresses can be

Evidence on the specific issue of the relationship of the and addressed as part of secondary prevention of CHD. For these reasons, life stresses need to be recognized

and death is limited and inconsistent. type A behaviour pattern to risk of recurrent CHD events

CHD. logic and pharmacologic) to the secondary prevention of of scientifically established approaches (non-pharmacoevidence. This idea is detrimental when it leads to neglect is contrary to an overwhelming mass of scientific important risk factor for first and recurrent CHD events The concept that "stress" is the key and most

OTHER FACTORS

ricopol

adherence to other secondary prevention advice. other systemic diseases. Heavy drinking also reduces pressure and weight over time, and its contribution to impairing left ventricular function, and increasing blood Excess alcohol intake is harmful because of its effect in grams of alcohol or two to three average drinks per day. general population. Moderation implies a limit of 40 tion should be advised for coronary patients as for the Abstention from alcohol or moderation in consump-

there is no evidence that alcohol improves the outlook

of the coronary patient.

The contraceptive pill

progesterone. They are the most frequent method of Oral contraceptives are made up of oestrogens and

1. Overweight should be reduced by caloric restriction (with a diet composition as set forth here), and exercise, to assist in the metabolic control of diabetes

and CHD risk factors.

2. Mortality and morbidity are higher for CHD patients with diabetes. Therefore, control of the major CHD risk factors (hypertension, hyperlipidaemia, and smoking) is particularly important in diabetics. With regard to diet this means:

a) Salt restriction, particularly by hypertensives.
b) Dietary fat modification in accordance with the

general guidelines given above.

c) High intake of vegetable fibre which contributes both to lowering serum lipids and better metabolic control of diabetes.

3. Thiazides and related diuretic drugs must be used wint care, because they may aggravate diabetes, raise serum lipids, and adversely affect serum potassium levels.

4. When beta-blockers are used, the possibility of masking symptoms of hypoglycaemia and of adverse effects on serum lipids must be kept in mind. In the treatment of insulin-dependent diabetics, beta₁-selective antagonists are preferred.

If impaired glucose tolerance — as defined in 1980 by the WHO Expert Committee on Diabetes Mellitus—is present, the above recommendations concerning CHD risk factor control apply.

Physical activity

Vigorous habitual physical activity has been associated with a decreased occurrence of coronary heart disease in several population studies but it has not been shown whether exercise alters the progression of CHD, nor is there evidence of an improved coronary collateral circulation in man.

In secondary prevention, however, dynamic exercise can be recommended to patients after acute myocardial infarction, coronary bypass surgery, or with angina pectoris for several reasons:

- 1. To combat the deleterious effects of immobilization.
 2. To improve physical working capacity and cardiovascular performance lower the levels of heart rate, arterial blood pressure, and rate-pressure
- product for the same submaximal physical load.

 3. To increase self-confidence and emotional stability, decrease deprescion and fear
- decrease depression and fear.

 4. To facilitate return to normal life (including work if
- appropriate).

 5. To improve weight control, joint mobility and stability and pentromuserular coordination.
- stability, and neuromuscular coordination.

 6. To encourage patients to modify other more powerful risk factors.
- 7. To induce favourable metabolic changes such as increase of HDL cholesterol relative to LDL cholesterol, decrease of triglycerides, and increase in sensitivity to insulin.

related to plasma levels of total cholesterol, low density (LDL) cholesterol, and to the ratio of LDL to high density lipoprotein (HDL).

Recommendations to reduce elevated plasma total cholesterol and low density lipoprotein (LDL) cholesterol by safe (particularly dietary) means —as part of the overall effort to improve prognosis of patients with atherosclerotic disease— are justified by many forms of evidence, including positive results from controlled trials. Changes in dietary fat composition may favourably influence both atherogenesis and thrombogenesis.

Optimal mean plasma cholesterol for adult populations is 5.2 mmol/l (200 mg/dl) or less, and an upper limit for individuals may be 5.7 mmol/l (200 mg/dl). Reduction of plasma cholesterol toward such levels can be achieved in most patients by:

1. Saturated fat intake of no more than 8-10% of calories; total fat no more than 25-30% of energy in take.

2. Cholesterol intake of no more than 200-250 mg/day for adults.

3. Ratio of polyunsaturated fatty acids to saturated fatty acids (P/S) of 0.75-1.00.

4. Dietary fibre intake of up to 30 g/day, derived chiefly from legumes, other vegetables, and fruit.

5. Gradual reduction of elevated body weight by restriction of energy intake (with attention to the qualitative recommendations above), and by

physical exercise (see appropriate section).

Extensive experience in many countries shows that eating patterns to achieve the foregoing nutrient levels

are both pleasant and widely acceptable.

While there are no data no whether treatment to increase levels of HDL will decrease risk, it is a prudent judgement that this change in plasma lipoproteins might also be helpful. Reduction of excess body weight, cessation of smoking, and suitable exercise often elevate plasma HDL. Similarly, the significance of isolated hypertriglyceridaemia is unclear, but this abnormality too is attenuated by these measures.

Familial hypercholesterolaemia and Type III hyperlipoproteinaemia often require drug treatment, in addition to diet, and vigorous attention to associated risk factors in view of the predisposition to premature atherosclerosis. Suitable combined therapy can lead to striking elerosis. Suitable combined therapy can lead to striking

reduction of lipid levels in such patients.

Correction of overweight lessens many recognized CHD risk factors and should be achieved by dietary restriction (with attention to the qualitative recommendations above) together with regular appropriate exercise.

Diabetes and impaired glucose tolerance

The treatment of diabetes (both insulin-dependent and non-insulin dependent) in patients with coronary heart disease (CHD) should be guided by the same principles as secondary prevention of CHD are the same in diabetics and non-diabetics. However, the following considerations are particularly important in diabetics:

patients with certain resting ECG abnormalities. of benefit or even possible harm from oral diuretics in indicates benefit, but there are also data suggesting lack CHD are complex. The main thrust of the evidence effects of treating high blood pressure in patients with The findings from the few controlled trials on the

Advice for hypertensive CHD patients

- continuous efforts to maintain adherence are of treatment regimen, careful follow-up, and 1. For the coronary patient with hypertension, flexibility
- first, wherever possible. pharmacologic measures should generally be applied with diastolic levels of 105 mmHg and above, nonelevated BP in the majority of patients, particularly 2. Though drug treatment may be required to correct particularly important.

These include:

- a) Reduction of overweight through caloric restric-
- b) Limitation of alcohol consumption
- c) Limitation of salt intake
- compatible with physical capacity d) A programme of regular moderate daily exercise

laemia, hyperlipidaemia, hyperuricaemia, and hyperpotential side effects of certain drugs as hypokadrugs, are important to minimize or prevent such with the appropriate choice of type and dosage of replace— these measures. These measures, along In case of need, drug(s) may supplement—but not

4. Since an excessive drop in BP may precipitate further blockers or calcium antagonists for angina pectoris). contribute to their preferential choice (e.g., betaused for other purposes for the coronary patient may 3. The blood pressure lowering effects of certain drugs glycaemia.

cardiovascular events, care should be exercised in

adherence to the prescribed regimen. important in achieving and maintaining long-term complaints and simplicity of the drug regimen are 5. Close and continuous attention to the patient's choosing a target level and in reducing BP.

Diet, plasma, lipids, and obesity

the underlying arterial disease, atherosclerosis, is directly to 3 extra events per 100 per year). Rate of progression of given year (e.g., a 90% change vs a 12% chance translates experiencing a major recurrent coronary event in any tisk means a substantial increase in the likelihood of attacks and death, even a "moderate" increase in relative CHD patients are generally at high risk of recurrent CHD, the absolute excess risk is similar or higher. Since is not as great for CHD patients as for people without (that is, the relative risk) with elevated serum cholesterol of large sample size, While the slope of increase in risk association are available from several follow-up studies and death in CHD patients. Data demonstrating this Hypercholesterolaemia is a risk factor for recurrent MI

> evidence that low tar, low nicotine cigarettes are less cularly in the former cigarette smoker. There is no and pipe smoking may also contribute to risk, parti-

smoking in patients with angina and in survivors of MI Published studies reporting the effects of cessation of

support the following conclusions:

- 1. Risks of satal re-infarction, sudden death and total
- 2. Risk of non-fatal re-infarction is reduced. mortality are lowered by 20% to 50%.
- continue over the long-term. 3. The benefits conferred by stopping smoking
- forms of smoking. coronary patients, irrespective of age, to discontinue all It is essential therefore for physicians to advise

Advice on stopping smoking

- not to smoke. smoking and should advise them, repeatedly if necessary, firmly inform CHD patients about the dangers of personnel should not smoke. They should positively and Hospitals and clinics should be no-smoking areas. Health the medical team of a committed and informed approach. 1. Success depends on the adoption by all members of
- 3. There is no evidence that sudden cessation of physicians is a most effective means of achieving success. induced to stop smoking. Advice to stop by the patient's confirm that up to 70% of post-infarction patients can be 2. Reports from risk factor intervention studies
- life-time cigarette smokers, smoking can have harmful effects, even in very heavy and
- 4. Advice about smoking should be provided as soon
- 5. The support of the family is important. as is feasible in the patient's illness.
- team members. However, such aids cannot replace patient, and in saving the time of physicians and their emphasizing advice, in informing and motivating the 6. Printed material and audiovisual aids help in
- resumption of smoking should be avoided, at least in the one cigarette, and circumstances which encourage the smoking. It is important to stress the risk of smoking even cessation rate and to help the patient from resuming support are necessary to achieve the highest possible 7. Long-term repetition of advice and continued personal advice.

hypertensive, may require specialist attention from a patients, particularly those who are obese and/or usually be prevented by careful counseling. Some such as weight gain, depression, or irritability, can The potential adverse effects of giving up smoking,

physician, dietitian, or psychologist.

earlier, vulnerable phase of abstention.

Hypertension

safest means possible (see below). and maintain control of high blood pressure (BP) by the prognosis. It is therefore a reasonable goal to achieve ot beiteler (linebendending in Telated to elevated blood pressure — average diastolic (5th phase) recovered from MI or with signs of other forms of CHD, Evidence is available indicating that in persons

Joint Recommendations on Secondary Prevention for Persons With Clinical Coronary Heart Disease*

encouraged by the substantial decline in coronary mortality which has occurred in several countries over the past decade. This reduction is almost certainly multifactorial in origin and reflects advances in both primary and secondary prevention of CHD. Recent experimental evidence pointing to the possibility of inducing regression, or at least retarding progression, of atherosclerotic sion, or at least retarding progression, of atherosclerotic prevention of CHD.

In the secondary prevention effort, account should be taken of the natural history of survivors of acute MI. In the first two months post-MI, the incidence of coronary death or reinfarction is extremely high — up to 40% of all such events in the first year. Patients with impaired ventricular performance, complex ventricular ectopy, or tricular performance, complex ventricularly high continuing ischaemia after MI are at particularly high risk for death or recurrent infarction during the first I to 2 years, and thereafter. For such patients, treatment (e.g., surgery, beta-blockers, calcium antagonists, anti-arrhythmics) should be tailored to the needs of their particular thmics) should be tailored to the needs of their particular subgroup, as subsequently specified.

While various drugs are important in the secondary prevention of CHD, emphasis should also be placed on hygienic means for improving the status of various coronary risk factors. A life-style should be emphasized that involves maintenance of non-obese body weight, regular exercise, reduction of dietary saturated fat and cholesterol, and avoidance of cigarette smoking and excessive alcohol intake. In developing approaches to secondary prevention, the physician often needs to intervene against several risk factors. For example, it makes little sense to reduce a patient's serum cholesterol level while not advising cessation of cigarette smoking. These measures apply equally to persons recovered tom myocardial infarction and to these who have anginatom myocardial infarction and to these who have anginat

from myocardial infarction and to these who have angina pectoris (AP) or electrocardiographic (ECG) or other signs of CHD.

It is not the intention of these guidelines to present

It is not the intention of these guidelines to present exact and comprehensive instructions. All measures suggested below should be applied considering the patient as a whole, especially his or her age, medical history and associated disease, as well as the possibility of drug interaction with multiple drug therapy.

SPECIFIC RECOMMENDATIONS

Smoking

Continued smoking is associated with increased risk of recurrent coronary episodes for patients with CHD, including those recovered from acute MI. The adverse effects of continued smoking may be dose-related. Cigar

In May 1980, at Kronberg/Taunus, Federal Republic of Germany, representatives of three Scientific Councils of the International Society and Federation of Cardiology (ISFC)—the Councils on Arteriosclerosis, Epidemiology and Prevention, and Rehabilitation of Cardiac Patients—developed a brief set of practical Joint Recommendations on Secondary Prevention for Myocardial Infarction Survivors. These recommendations, widely reprinted and circulated, were broadly useful for practitioners taking care of patients after myocardial infarction(MI).

The present document is an update of the Kronberg statement. Four developments led to the need for such an update: the continuing surge of new knowledge from multiple research disciplines, new reports from randomized controlled trials assessing efficacy of various projected treatments for patients with coronary heart disease (CHD), establishment of an active Council on Clinical Cardiology by the ISFC, constructive comments and queries to the ISFC and its Councils on the 1980 Joint Recommendations.

Recognizing the potential value of an up-dated set of Joint Recommendations, the Chairman of the ISFC Council on Arteriosclerosis, joined by the Chairmen of the Councils on Clinical Cardiology, Epidemiology and Prevention, Rehabilitation, and of the ISFC Scientific Board, took the initiative to organize a meeting of 46 scientific experts from the four Councils. The group worked in plenary and small panel sessions.

The resultant up-dated Joint Recommendations on Secondary Prevention for Persons with Clinical Coronary Heart Disease, The product of these deliberations, were approved in the concluding plenary session of the Titisee meeting, and edited for publication in professional journals by the afore-mentioned five Chairmen.

econdary prevention of coronary heart disease (CHD) includes all measures aimed at preventing deterioration and death, applied to persons with clinically manifest CHD.

Secondary prevention is seen as an essential part of an overall strategy and policy for the prevention of CHD. Efforts toward the prevention of CHD have been

Federation of Cardiology. *Reprinted from Heart Beat, Journal of the International Society and Federation of Cardiology, 1984.

By the ISFC Scientific Councils on Arteriosclerosis (Chairman: Dr. G. Schettler, Heidelberg, FRG), Clinical Cardiology (Chairman: Dr. E. Rapaport, San Francisco, USA), Epidemiology and Prevention (Chairman: Dr. K. Pyorala, Kuopio, Findand), and Rehabilitation (Chairman: Dr. K. Konig, Waldkirch, FRG). Workshop of the International Society and Erderalion of Cardiology.



DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C.* Angel Espinosa-López, M.D.* Ivette D. Rico-Pagán, M.D.**

Una niña de 16 meses de edad se hospitaliza para estudios diagnósticos invasivos por un soplo cardíaco y cianosis detectados con dos meses de anterioridad. No hay evidencia de insuficiencia cardíaca ni de episodios hipóxicos en su historial pasado. Su crecimiento y desarrollo pueden considerarse adecuados para su edad.

Al examen físico se aprecia una niña bien nutrida, asintomática y con signos vitales normales. Se puede observar cianosis circumoral y sub ungueal con dedos hipocráticos. Tiene abombamiento discreto del hemitorax izquierdo con un precordio activo, accesibilidad ventricular izquierda y un PMI en el 5° espacio intercostal izquierdo a nivel de la línea axilar anterior. Hay un frémito grado II en el $3-4^{\circ}$ espacio intercostal en el margen esternal izquierdo. A la auscultación se aprecia un soplo sistólico-eyectivo, rudo, grado 4/VI en el 2-3er. espacio intercostal al nivel del borde esternal izquierdo. No hay componente diastólico. El S_1 es normal, el S_2 está sencillo y se ausculta un S_4 en la región apico-esternal. Hay hepatomegalia (4cm) no dolorosa, no hay edema y los pulsos periféricos son normales en todas las extremidades.

La hemoglobina es de 13.5gm y el electrocardiograma es compatible con hipertrofia ventricular izquierda, agrandamiento atrial izquierdo y un eje QRS desviado a la izquierda (-30°). La radiografía de torax demostró cardiomegalia con agrandamiento atrial derecho, aorta prominente e hipovolemia pulmonar.

A continuación se ilustran tres vistas de su angiocardiograma:



Figura 1. Atriograma derecho, proyección frontal. Las flechas señalan el área de la válvula mitral. VCI = vena cava inferior, AD = atrio derecho, AO = aorta, AI = atrio izquierdo, VI = ventrículo izquierdo.



Figura 2. Ventriculograma izquierdo. Las flechas señalan la comunicación interventricular. AP = arteria pulmonar.



Figura 3. Ventriculograma izquierdo, proyección lateral

¿CUAL ES SU DIAGNOSTICO?

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Atresia tricuspídea Tipo IB

En la atresia tricuspídea hay agenesia completa de la válvula tricuspídea de manera que no existe comunicación directa entre el atrio derecho y el ventrículo del mismo lado. Además hay un defecto inter-atrial, hipoplasia del ventrículo derecho y una comunicación entre la circulación pulmonar y la sistémica, casi siempre por medio de un defecto del septo interventricular (VSD).

Se puede decir que la atresia tricuspídea (AT) es un defecto poco común. En la mayoría de las series grandes de cardiopatías congénitas la AT comprende sólo un 2% de las mismas.^{1, 2}

La AT está invariablemente asociada a otras cardiopatías. Estas cardiopatías pueden ocasionar que el flujo pulmonar esté normal, disminuído o aumentado, afectando así la hemodinamia y las manifestaciones clínicas de esta cardiopatía. Ello determinará también el tipo de tratamiento que se requerirá. Para categorizar los diferentes tipos de AT se utiliza una clasificación propuesta por Kulme en 1906 y luego modificada por Edwards en 1974.³ Una versión simplificada de ella se ilustra en la tabla I, donde podemos observar que hay dos tipos principales: uno con relación normal de los grandes vasos (tipo I) y el otro con d-transposición de las grandes arterias (tipo II). Cada tipo se divide a su vez en varios sub-tipos dependiendo si hay estenosis pulmonar (PS) o atresia, y la ausencia o presencia de un VSD. Hay un tercer tipo, menos frecuente que los demás, que lo constituyen aquellos pacientes con AT y L-transposición de los grandes vasos.

Tabla I

Tipos de	Incidencia*	
Tipo I.	Relación normal de los grandes vasos	
	a. Septo interventricular intacto y	
	atresia pulmonar	9%
	b. Comunicación interventricular pequeña y	
	estenosis pulmonar	51%
	c. Comunicación interventricular grande sin	
	estenosis pulmonar	9%
Tipo II.	D-transposición de los grandes vasos	
•	a. Comunicación interventricular con	
	atresia pulmonar	2%
	b. Comunicación interventricular con	
	estenosis pulmonar	8%
	c. Comunicación interventricular sin	0,0
	estenosis pulmonar	18%
Tipo III.	L-transposición de los grandes vasos	3%

*Serie de 143 pacientes del Children's Hospital Medical Center, Boston, Mass.

La cianosis es el signo más frecuente en la AT y resulta del corto circuito obligatorio de derecha a izquierda a través de una comunicación interatrial. La intensidad de esta cianosis dependerá de la magnitud del flujo pulmonar, siendo más intensa en aquellos con AT y septo interventricular intacto o PS severa. Es menos marcada en aquellos tipos de AT con buena comunicación intraventricular y/o arteria pulmonar grande (Ic y IIc) donde el cuadro clínico predominante será el de fallo cardíaco, el cual es particularmente difícil de controlar aún con medicamentos.

La auscultación en la AT es más bien inespecífica y va a depender de la severidad de los defectos cardíacos congénitos que le acompañan. El soplo regurgitante de VSD y/o PS se aprecia cerca del margen esternal izquierdo, el S₁ y S₂ son por lo regular sencillos y ocasionalmente puede escucharse un "click" eyectivo. Cuando la comunicación interatrial no es adecuada puede apreciarse una onda "a" prominente en el pulso venoso yugular así como un S₄ en la auscultación. Los hallazgos radiográficos en la AT también van a depender del "status" de las cardiopatías asociadas, pero por lo regular se puede apreciar: cardiomegalia y silueta cardíaca de configuración izquierda, concavidad en el área de la arteria pulmonar e hipovolemia pulmonar. En cambio, en la AT tipo Ic y IIc el segmento de la arteria pulmonar y la vascularidad pulmonar están prominentes. La tríada electrocardiográfica de agrandamiento atrial derecho, con ondas P altas (>3mm) y picudas, hipertrofia ventricular izquierda y desviación a la izquierda del eje eléctrico de QRS es casi diagnóstica de AT.

Los episodios hipóxicos ocurren en un 15-45% de los infantes con AT, usualmente son infantes menores de 6 meses de edad y con hipovolemia pulmonar. Su aparición usualmente está relacionada a una disminución o cierre espontáneo del VSD, a estenosis pulmonar severa o progresiva o debido al cierre de un ducto arterioso patente.^{4, 5} La fisiopatología de estos episodios es similar a los que vemos en pacientes con tetralogía de Fallot y constituyen un signo siniestro pues implica un flujo pulmonar críticamente disminuido y es necesario cirugía con carácter urgente.

Los infantes con AT y cianosis severa o policitemia están predispuestos a accidentes cerebrovasculares. Aún se describen casos de abscesos cerebrales en 2-5% de estos pacientes, constituyendo una complicación seria y potencialmente fatal. Debido al corto circuito obligatorio intracardíaco de derecha a izquierda se obvia la acción fagocítica "filtrante" de la trama capilar pulmonar y bacteremias transitorias pueden colonizar el tejido cerebral previamente alterado por hipoxia y producirse por consiguiente el absceso. Debe siempre sospecharse un absceso cerebral en todo paciente cianótico mayor de 2 años de edad con cefaleas, convulsiones o signos neuro-lógicos focales. Esto también constituye una situación de emergencia pues requiere aspiración y tratamiento agresivo con antibióticos.

El diagnóstico de AT se logra mediante la angiocardiografía. El atriograma derecho (fig. 1) demuestra un atrio derecho grande, con reflujo a la vena cava inferior, opacificación del atrio izquierdo y luego del ventrículo izquierdo grande a través de la válvula mitral. Puede apreciarse el "suelo" del atrio derecho intacto sin que se opacifique el tracto de entrada ventricular derecho. Esta sombra negativa o "ventana" ventricular derecha creada por la falta de opacificación del ventrículo derecho es característica de la AT.⁷ El ventriculograma izquierdo en posición frontal y lateral (fig. 2 y 3) es esencial para la identificación del ventrículo derecho hipoplásico, para la visualización del VSD, así como para evaluar las arterias pulmonares, el tipo de obstrucción pulmonar existente y la relación de los grandes vasos.

El tratamiento de la AT es quirúrgico. La cirugía

paliativa para la AT está encaminada a mejorar el flujo pulmonar cuando está disminuido.

Los neonatos con hipoxemia severa, y cuyo flujo pulmonar depende totalmente o en parte de la patencia del conducto arterioso se benefician enormemente con la infusión de prostaglandina E₁. Con ello se dilata el ducto arterioso, aumentando el flujo pulmonar con lo que se mejora la oxigenación y se estabiliza el infante en lo que se realizan los estudios diagnósticos y la cirugía paliativa. Esta cirugía paliativa en el período neonatal se logra mejor creando un corto circuito aorto-pulmonar central utilizando material prostético como los tubos de Gore-Tex. Luego del mes de edad el procedimiento paliativo de elección es la anastomosis de Blalock-Taussig que consiste de una anastomosis entre la arteria pulmonar y la subclavia. Recientemente en infantes de bajo peso y arterias de pequeño calibre se ha venido utilizando material prostético en la anastomosis de Blalock-Taussing con resultados excelentes e incidencia baja de oclusión.

La experiencia quirúrgica con un procedimiento fisiológico en la AT ha sido muy alentadora. Este es el procedimiento de Fontan, que consiste en anastomosar la arteria pulmonar y el atrio derecho (por anastomosis directa o conducto prostético) con cierre del defecto interatrial y ligando la arteria pulmonar a nivel supravalvular inmediato.8 Con ello se canaliza el retorno sistémico venoso directamente al pulmón. Existen otras modificaciones del procedimiento original descrito por Fontan, diseñadas específicamente para cuando hay un ventrículo derecho que no está hipoplásico. En esos casos además de lo anterior se cierra el VSD y puede colocarse un conducto prostético entre el atrio y el ventrículo derecho con o sin válvula. Sin embargo, no todos los pacientes con AT cualifican para esta reparación fisiológica pues hay unos criterios que deben cumplirse para poder recomendarla. Los más importantes son:

- niños entre 4 y 15 años de edad
- resistencia vascular pulmonar normal y presión pulmonar media menor de 20 mmHg
- tamaño adecuado de arterias pulmonares (diámetro de 75% o más que el de la aorta)
- función ventricular izquierda buena
- ritmo sinusal normal

Haciendo una selección más cautelosa de pacientes para la corrección fisiológica de la AT se ha logrado reducir la mortalidad del procedimiento de un 14% en 1978 a menos de 7% en 1981. En estos pacientes que han sobrevivido se ha observado una mejoría dramática tanto en sus síntomas como en la calidad de vida que pueden llevar a cabo luego de la cirugía.

La sobrevivencia de pacientes con AT hasta la segunda década de vida es de un 50% en aquellos casos con un manejo adecuado. Esto contrasta grandemente con la sobrevivencia de sólo 10% (hasta la segunda década) en aquellos sin cirugía. Solo algunos casos excepcionales, como los revisados por Johnson, 10 pueden llegar a la tercera década.

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CARTAS AL EDITOR

A través del último año hemos tenido cambios grandes en la práctica médica, muchos más profundos a mi entender, que lo que puede suponerse a primera vista.

Tenemos auditoría a nivel de nuestra oficina. Ese recinto que es nuestra segunda casa, y algunos dirán es la primera, pues habitamos en ella más que la verdadera... ahora se convierte en área abierta para el cotejo escudriñante del asegurador. Así, en otra parte se le pide a un representante de "medicare" permiso para ingresar un paciente para una resección transuretral de próstata. ¿Qué nos ha llevado a esta penosa situación? ¿Están abusando con el médico estos grandes y poderosos imperios de seguros médicos y se sigue al pie de la letra la infame y nefasta disposición de quien tiene el dinero hace la ley?

¿O es a la inversa? Que hemos abusado nosotros y son ellos las que se estan defendiendo. Uno no puede vivir sin el otro y por reglamentación ajena a nosotros hay algo que se brinda como explicación para su implementación. Reglamentaciones que insinuan una falta de confianza en la seriedad médica nuestra y un juramento hipocrático vacío y vano, una afrenta a nuestra verticalidad.

Pero, si lo dicho antes es fuerte, también lo es enterarse que hay mercaderes de salud, que utilizan como fuente de lucro lo que tiene que ser brindado con el alma. No empañemos esa relación médico paciente de inspiración divina con la burla de una farsa.

Tenemos soluciones en nuestras manos 1) Que nosotros los urólogos demos el ejemplo de rectitud, de manera que podamos respaldar cualquier afrenta con un historial nítido de decencia médica. 3) Ser exquisitamente selectivo en escoger candidatos a urólogos hasta donde sea posible, a segurándonos que llenen nuestros requisitos. 3) Que cooperemos con las autoridades pertinentes para desenmascarar aquellos que no cumplen con los canones básicos de ética médica.

Yo soy un optimista y no percibo un futuro desvastador, sino al contrario, lleno de alternativas. Estamos en un "high" médico. Existen hoy en día adelantos en métodos de diagnósticos y tratamiento ni siquiera soñados hace quince, diez, o cinco años atrás. ¿Y los que faltan? El advenimiento de técnicas con laser, los adelantos en quimioterapia, el perfeccionamiento de las técnicas de endourología y las vacunas contra cierto tipo de cáncer son solo algunas de las que vislumbra el futuro.

Así que vamos a practicar medicina como se debe, pues la clase médica cuenta con un historial de dos mil años, que va desde que el sabio médico Hipócrates dio su juramento, hasta los grandes adelantos de hoy, como ejemplo de dedicación, vocación, altruísmo y compasión hacia el enfermo.

José L. Ferrer, M.D. Presidente Saliente Puerto Rico Urological Association Una vez más aparece en el Boletín (febrero 1985) un comentario (editorial) sobre las deficiencias del Centro Médico de Río Piedras y una vez más se culpa a un presupuesto insuficiente como la causa principal. Y yo, una vez más, me tomo la libertad de señalar que la razón de su deficiente funcionamiento no se debe tanto a la falta de dineros como a su diseño estructural y, consecuentemente, operacional. La falla descansa en su sistema que se cuestionó desde que se planeó.

Ya pueden asignarle al Centro Médico los millones que quieran; todos se los "chupará" como una esponja de infinita hidrofilia. De hecho, todos sabemos que el presupuesto con el que cuenta hoy el Centro Médico alcanza muchos más millones que los que les fueron asignados en sus primeros años. Sin embargo, la eficiencia sigue brillando por su ausencia y su déficit sigue creciendo.....

Cuando el Dr. Vázquez-Quintana se expresa sobre el Hospital Universitario y el Hospital Pediátrico, pone el dedo en la llaga al sugerir que "se debe autorizar la construcción de salas de operaciones en ambos hospitales y descentralizar algunos servicios". Y yo añado: descentralizar las instituciones junto con la mayoría de los servicios. Bien dice el Dr. Vázquez-Quintana que estos hospitales "son instituciones cautivas del Centro Médico". Sus Facultades tienen, por obligación, que trabajar con las manos atadas, pendientes de las decisiones de la maquinaria burocrática del Centro Médico que controla, entre otras funciones, el desembolso de los dineros.

Termina el editorialista abogando por arbitrios adicionales para destinarlos al financiamiento de los tres Centros Médicos de la Isla. Yo no estoy al tanto de la situación de los Centros de Ponce y Mayagüez, y desconozco la existencia de la mencionada Escuela de Medicina de Mayagüez. Por ello es que solamente comento sobre el Centro Médico de San Juan (R.P.). Dice el distinguido cirujano que de no contar con estos recursos financieros adicionales, el Centro Médico está destinado al fracaso. No, Dr. Vázquez-Quintana. Este Centro Médico estaba abocado al fracaso desde que se inauguró. Ha seguido operando porque, sencillamente, pertenece al Gobierno.

José M. Torres-Gómez, M.D., F.A.C.P., F.A.C.C.



ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., F.A.C.C.

Figures 1 and 2 are Doppler blood flow velocity (V) tracings obtained from two different subjects, using a Honeywell echocardiograph (Biosound. Indianapolis, Ind), with two-dimensional echocardiographic and pulsed-wave Doppler (PWD) equipment, which provides simultaneous two-dimensional images and Doppler flow velocity curves.

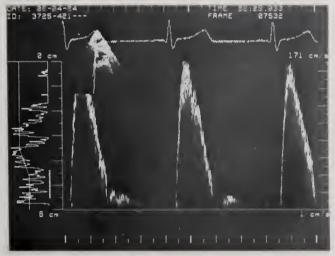


Figure 1

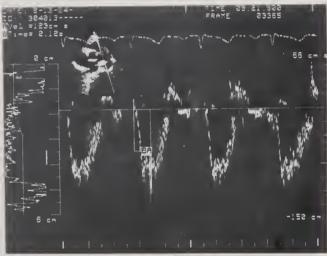


Figure 2

Questions

- 1. Identify the origing or site of the pulse tracings.
- 2. Where is the sample volume (SV) located?
- 3. Where is the transducer located?
- 4. What are the flow velocities? Are they normal?
- 5. How can blood flow volume, cardiac output, be determined from the Doppler flow curves?
- 6. Is pulmonary hypertension (PH) present in Case 2?

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Answers

Figure 1, Case 1, is a suprasternal notch (SSN) long-axis freeze-frame view with the SV positioned in the ascending aorta (AAo) (see left upper insert). Time markers are located along the top and bottom margins of the print (between the heavy lines is 1 second-S). An electrocardiogram is present above the pulse traces. On the left side, there are an A-mode trace with ramp settings and gain, and depth calibration scale in cm. On the right side is a flow V calibration scale (each longer horizontal line = 20 cm/S V level) in cm/S. The SV is positioned at a depth of 5 cm from the scanhead, parallel to blood flow.

Systolic positive flow (toward the transducer) above the zero baseline is present. The peak flow V = 1.8 M/S. The flow curves are those of a normal tracing and are ideal manifesting only the sharp, well-delineated envelope of the high flow velocities, with minimal spectral dispersion. The acceleration time (AT), from onset of trace to peak, is rapid (85-90 mS), the deceleration time (DT), from peak to end of trace, is 200 mS, the total ejection time (ET) is 290 mS. The small early diastolic flow may reflect blood filling the sinuses of Valsalva and coronary arteries, and negative eddies/velocities; the reversal of flow necessary to close the valve.

Figure 2, Case 2, is a parasternal short-axis still-frame view (see left upper insert) of pulmonary artery (PA) blood flow V with the SV positioned into the main PA, 3.5-4 cm from the scanhead. The format is similar to that of Figure 1. The systolic negative flow curves represent pulmonary flow, and possess rather "clean" flow velocity envelopes of higher flow velocities; minimal spectral dispersion is present. A negative presystolic velocity "a" wave (equivalent to a pulmonary valve "a" wave) reflects actual flow in the PA. Small, brief early diastolic, positive flow is often observed in normal subjects. Also, a notch on the downstroke of the curve is a common artifact. The peak systolic flow V is 1.35 M/S. This can be instrument-derived automatically. The time-to peak V (TPV) or AT of the PA curve is instrument-derived by manual placement of a time cursor on the trace as illustrated. It is 120 mS, which is normal.

The PA is studied from the left sternal border or SSN. The PA curve is more rounded with a late peak V. Exact location of the SV in the PA is important because different pulse contours may be obtained depending on SV location. Pulmonic valve movements serve as landmarksdark lines on the traces (aortic and mitral valve movements).

Systemic (Ao) -cardiac output- and PA blood flow volumes may be computed automatically by the instrument or manually, from the digitized flow V curves and the cross-sectional area of the Ao and PA (intervessel diameter measurement is offered by the two-dimensional parameters, as well by M-mode and A-mode echocardiography). The Ao orifice diameter has been recommended as it is the smallest and has a flat V profile and the highest Vs. The Ao diameter and flow are preferentially obtained form the SSN, but subcostal, apical left ventricular (LV) outflow tract, high right parasternal or precordial long axis views can be utilized. Audio steering, two-dimensional imaging or a "blind" M-mode mapping

technique with a right-angled probe (3-12 cm depth with variable transducer angulation) are applied seeking the maximal signal frequency (a clean signal, continous, with musical whistling character, the highest pitch and narrow band of frequencies with few low frequencies), strength and velocity with an ET between 180-300 mS. This is usually at a depth of 11 cm in adults for the AAo, which is anterior and slightly to the right. The descending Ao (DAo), posteriorly and slightly to left is less than ideal and the Ao arch should be avoided. The SV is placed in the central AAo lumen as the curve contours differ in the lateral and medial positions- V profile is not flat the center line may reflect the mean. Systolic fluttering and clicks may be found at the aortic valve level. Valve movements are heard as sharp clicks and observed as spikes on the velocity traces. The Doppler signal itself may be the best indicator of flow direction (Hatle). Ao flow curves are altered in various heart lesions, in decreased cardiac output, cardiac arrhythmias and in normal subjects. A 2.5 MHz transducer has proven useful. Continous wave Doppler (CWD) has been recommended to be used first and then PWD. A low frequency Doppler is utilized if the V limit is exceeded.

Flow = $\frac{\text{mean V/beat X beat x orifice area}}{\text{Cosine O}}$ or $\frac{\text{mean V in cm/S x flow area in cm}^2 \text{ x 60 S/min}}{\text{Cosine O}}$ O = beam-flow or intercept angle.

area of a circle = πr^2 , radius (r) = $\frac{\text{diameter}}{2}$

Measure flow in a laminar stream, not in a jet or area of disturbance. Ao flow correlates well with PA and tricuspid flows. Cardiac output by Doppler correlates with that by the thermodilution or Fick methods. V is higher across all the valves in the presence of augmented cardiac output or stroke volume. Recently, new methods for determination of stroke volume and cardiac output, have been described from an apical 4-chamber window (mitral inflow and LV outflow).

Ao and PA flows normally are laminar, smooth and display narrow spectral bands from uniform Doppler shifts. The Ao trace manifests an abrupt rapid narrow acceleration phase in early systole and a slightly slower deceleration phase during late systole, and an overshoot below zero baseline in early diastole. Minor spectral broadening may occur at the peak and during the deceleration phase.

Obtain maximal and mean Vs and amplitudes. The peak flow V is measured at the top of the heaviest signal of the V trace- vertical V in cm/S, horizontal time in S. Average V can be obtained by planimetry or digitization of the areas under the curves (flow-V integrals) and by computer. The systolic V integral is the area under the systolic V envelope, not the peak V.

Normal Velocities and Times:2, 6-8

V (cm/S) mean range max.	ET (mS)	AT	DT	Average Acceleration (peak flow V) AT	Deceleration (peak V) DT
Ao 88.5,135 (60-170) in adults. 150 (120-180) in children.	295	98 (83-118)	197 (170- 230)	940	473
PA 75 (60-105) in adults. 90 (70-110) in children.	331	159 (130-185)	172 (148- 208	396	356

Thus, the peak flow V and average acceleration and decelerations are higher, and the ET and AT shorter in the Ao than in the PA. Vs are normally faster in children than in adults.

Mean PA pressure and resistance may be evaluated by:

- 1. Pulmonary Flow V Curve- TPV is the time between onset to peak V of the PA Doppler flow trace. Normal > 100 mS. PH < 100 mS.
- 2. Estimated by 80 $\frac{\text{TPV}}{2}$ = mean PAP in mm Hg.
- 3. Absent negative presystolic "a" wave.
- 4. TPV/ET of right ventricle (RV)-correlates negatively with systolic PA pressure. Normal 0.35-0.53; less with PH.
- 5. Preejection period (PEP), RVET and PEP/RVET ratio can be determined from a Doppler PA V tracing. Normal < 0.34; prolonged with PH.
- 6. Prolonged RV isovolumic relaxation time.
- 7. High V and long duration of tricuspid regurgitation, (TR) and late opening of tricuspid valve. High V in pulmonic regurgitation. Maximal V across shunts. Calculated pressure differences across TR, ventricular septal defect, RV outflow tract obstruction and patent ductus arteriosus.
- 8. Ao curve- may have a slower increase in V and a later peak, etc.

Doppler velocities and cardiac outputs are useful, reliable and reproducible, and are valuable in the management of critically ill patients, in the CCU, ICU, catheterization laboratory, operating and recovery rooms, for evaluation of drug, fluid and Peep (settings) therapy, for determination of the correct cardiac pacemaker mode, rate and AV interval settings, for determination of valvular stenosis gradients and valve areas, shunt evaluation, localization of cardiac murmurs, for evaluation of myocardial performance and ejection dynamics- rate, V of flow and regurgitation, and for its portable bedside applications.

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What can you do for hypertensives like these?



Rely on one-tablet-a-day for these and virtually

Laura K is depressed ... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN* (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits ...will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Smoking has been implicated—especially in males. Cardioselective TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence. Only 0.4% of patients in the 28-day TENORMIN

evaluation program

reported sexual performance problems.3 At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments. Although beta blockers may mask tachycardia occurring with hypoglycemia. TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood same degree as

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen. Unlike propranolol, cardioselective TENORMIN can reduce the likelihoo of bronchospasm in susceptible patients. 5.6



dosage and cardioselectivity all your hypertensives.

rorkup shows 62/100 mmHg. On imetidine for pepculcer. Don States the thought of yet another medication.

ENORMIN is not metabolized by the eyer. Its pharmaconnetics are unaffected when it is dministered consomitantly with metidine 7.8 or

ewly diagnosed...



"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹⁰



*Cardioselectivity denotes a relative preference for eta, receptors, located chiefly in cardiac tissue. This preference is not absolute.

TENORMIN® (atendol)

See following page for brief summary of prescribing information.





Therapy for virtually every hypertensive patient in your practice.

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[1-methylethyl) amino] propoxy]-. Alenolol (free base) has a molecular weight of 266 ft is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C). and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diurteric.
CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.
Ischemic Heart Disease: Following abruptic resistation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do n

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery in this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloredthylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE) Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosts: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked brady-cardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and cloridine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clondine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the province of t

the maximum recommended human dose) was unaffected by atendol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atendol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose,

The respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-respectively.

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. IENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolo.

atenciol.

Pediatric Use: Safety and effectiveness in children have not been established
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates
were derived from controlled studies in which adverse reactions were either volunteered by the
patient (U.S. studies) or elicited (eg. by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when
these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebois similar, causal relationship is uncertain.

these reactions were volunteered Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), itredness (0.6%-0.5%), fratique (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.0%), depression (0.6%-0.5%), dreaming (0%-0.0%)
ASSTROINTESTINAL diarrihea (2%-0.0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0.0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL: diarrihea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMINI (atenolol).

TENORMIN (atenoid):

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional liability with slightly clouded sensorium, decreased performance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

reaction

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Fallure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, soproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

Bronchospasm: Aminophylline, isoproterenol, or atropine.
Hypoglycemia: Intravenous glucose.
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit. TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type duretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1 73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage	
15-35	16-27	50 mg daily	
<15	>27	50 mg every other day	

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolo); round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly callendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolo); round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

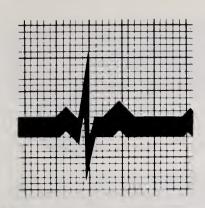
Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Pharmaceuticals.



STUART PHARMACEUTICALS

Division of ICI Americas Inc. Wilmington, DE 19897



ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, MD, FACC

This 18-year-old male underwent cardiac surgery 5 years previously. Four and one-half months prior to death he suffered severe headaches, dizziness, dyspnea and weakness. About 18 days before death he became deeply blue, apneic, had blurred vision and lost consciousness. He recovered with oxygen. Chest pain and cough with yellow sputum occurred. Procrastination had prevailed in respect to cardiac catheterization and follow-up care. The patient was poorly developed. Cyanosis, injected conjunctivae and clubbing were obvious. There was a grade 2-3 systolic, ejection murmur at the pulmonic are which radiated to the entire precordium. Levoscoliosis was evident. A roentgenogram showed normal heart size and pulmonary blood flow. Hb ranged from 13.6 to 25.5 g/dl, and Hct from 69-80.8%; MCV was 72 u³ and MCH 23 uug.

Three pints of blood were removed because of "hyperviscosity symptoms". Three liters of normal saline were infused; the Hct decreased from 71 to only 68%. Three days later he was found unconscious, apneic and cyanotic. Oxygen with Ambu was administered. Blood gases denoted metabolic and respiratory acidosis (pH 7.05, pO₂ 25 and pCO₂ 62 mm Hg, base excess -13 mm/L); bicarbonate was administered and another phlebotomy performed. Packed red cells, 250 cc, were transfused to improve oxygen carrying capacity! The next day the patient became lethargic, hypothermic and shocky, with respiratory distress. Oxygen and additional bicarbonate were administered. He expired after attempts at intubation.

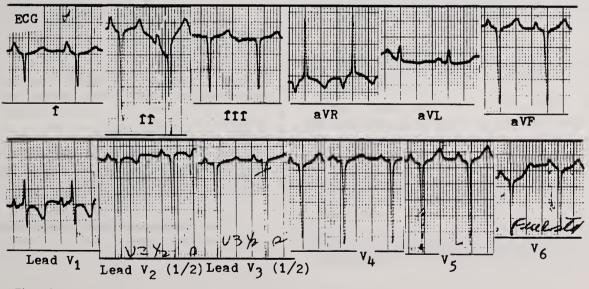


Figure 1

Questions

- 1. What are the electrocardiographic diagnoses?
- 2. Suggest possible clinical diagnoses.

Answers

Pentalogy of Fallot. He was cyanotic shortly after birth, and subsequently squatted and was intolerant to exercise. Cardiac catheterization 9 years previously revealed an atrial septal defect (ASD), ventricular septal defect (VSD), a small right ventricle (RV) and infundibular pulmonic stenosis.

Right atrial enlargement (RAE).

Marked right ventricular hypertrophy (RVH).

Marked right axis deviation (RAD) (superior, northwest axis, near = 240°)

Comments

Pentalogy of Fallot comprises tetralogy of Fallot (TF) plus an ASD. ASD or patent foramen ovale is common in TF.

The electrocardiogram (ECG) of typical TF may demonstrate RVH of pressure overload or strain, RAD, uncommonly right bundle branch block (rsR or slurred R patterns are frequent), wide QRS-T angle (or upright T waves in V_{1-2} of severe TF in neonates) and ST segment shift, sometimes RAH (P pulmonale) and the precordial "double transition sone" of Sodi-Pallares. The vector-cardiogram (VCG) shows a large oval, inferior, anterior rightward clockwise type A loop with a discordant T loop. Atrial flutter or fibrillation and ventricular arrhythmias have been observed. Atypical TF may demonstrate combined ventricular hypertrophy (LVH) (dominance).

PF may present a similar ECG as does TF, or may manifest LAD, RVH of volume/diastolic overload type with small q waves in leads I, a VL, V₃-₅ and upright T waves in leads V₂₋₆. Severe RVH with an increased magnitude of the initial septal vector, and a counterclockwise frontal VCG loop reflect IV overload secondary to the right-to-left shunt at the atrial level.

Possible causes of such posterior vectors are: the pressure relationships, malalignment of the heart, distortion of the conduction system, chest deformities and lung factors, etc.

Sole RVH due to obstruction to pulmonary flow may show a small r and deep S waves in leads V₁, V₁₋₃ (mimicking LVH) or in all precordial leads including V₄R. Single or common ventricle may present an ECG with posterior forces, as a repetitious rS pattern in all the precordial leads; other conditions are corrected transposition of the great arteries with VSD, ostium primum ASD, TF, emphysema (S₁, S₁₁, S₁₁ pattern), and extensive anterolateral myocardial infarction. Magnitude of S waves greater than r waves in the S₁, S₁₁, S₁₁₁ syndrome, indicate severe congenital RVH.

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SOCIOS NUEVOS



ACTIVOS

Aybar Quijano, Héctor E., MD - Universidad Católica Madre y Maestra, Santiago, República Dominicana, 1982, Medicina General. Ejerce en Mayagüez.

Colón Rodríguez, Manuel, MD - Universidad Autónoma Guadalajara, México, 1978, Obstetricia y Ginecología. Ejerce en Arecibo.

De Jesús Tejada, Víctor, MD - Universidad Autónoma de Santo Domingo, República Dominicana, 1976, Medicina General. Ejerce en Santurce.

Feliciano Valera, Ricardo, MD - Universidad Central del Caribe, Cayey, 1981, Anestesiología. Ejerce en Río Piedras.

Flores Rodríguez, Eduardo, MD - Universidad de Salamanca, España, 1970, Pediatría. Ejerce en Caguas.

Frontera Rodríguez, Herminio, MD - Georgetown University, Washington, DC, 1976, Medicina Interna. Ejerce en Río Piedras.

Gago Rivera, Jorge, MD - Universidad Autónoma de Guadalajara, México, 1977, Medicina General. Ejerce en Santurce.

Gandía Mántaras, Luis T., MD - Universidad Central del Caribe, Cayey, 1981, Medicina Interna. Ejerce en Isla Verde.

González Inclán, José Raúl, MD - Harvard Medical School, Boston, Mass., 1972, Cirugía. Ejerce en Hato Rey.

Hernández Aponte, Gloria Esther, MD - Universidad Central del Este, República Dominicana, 1979, Medicina General. Ejerce en San Lorenzo.

Jirau Toledo, Aquiles, MD - Unversidad Autónoma de Santo Domingo, República Dominicana, 1974, Anestesiología. Ejerce en Río Piedras.

Maestre Grau, Bárbara, MD - Universidad de Puerto Rico, 1977, Patología Clínica y Anatómica. Ejerce en Hato Rey.

Malavé, Aixa M., MD - Universidad de Michigan, 1977, Patología. Ejerce en Ponce.

Maldonado González, Antonio, MD - Universidad Autónoma de Guadalajara, México, 1976, Radiología. Ejerce en Arecibo. Miranda Ferrer, Manuel N., MD - Universidad Autónoma de Barcelona, España, 1980, Oftalmología. Ejerce en Caguas.

Rivera Jiménez, Enid, MD - Universidad de Puerto Rico, 1981, Pediatría. Ejerce en Caguas.

Santos Torres, Armando J., MD - Universidad Central del Caribe, Cayey, 1980, Pediatría. Ejerce en Caguas.

Soares Rivera, Manuel, MD - Universidad de Puerto Rico, 1978, Ortopedia. Ejerce en Humacao.

Soto Tapia, Edwin, MD - Universidad Central del Este, República Dominicana, 1976, Pediatría. Ejerce en Arecibo.

Spickers Santiago, Albert, MD - Universidad de Santiago de Compostela, España, 1978, Medicina General. Ejerce en Toa Baja.

Suárez Domínguez, Albert, MD - Universidad de Puerto Rico, 1972, Cirugía. Ejerce en Río Piedras.

ACTIVO NO RESIDENTE

Fernández Lugo, Orlando Sixto, MD - Yale Medical School, 1979, Ortopedia. Ejerce en Boston, Mass.

INTERNOS RESIDENTES

Acosta Azcona, Clara, MD - Universidad Autónoma de Santo Domingo, República Dominicana, 1976, Medicina Interna.

Collado Marcial, José Luis MD - Universidad Autónoma de Guadalajara, México, 1977, Medicina Interna.

Johnson Fernández, Sylvia P., MD - Universidad de Zaragoza, España, 1976, Psiquiatría.

Sánchez Fernández, Jorge A., MD - Universidad Central del Este, República Dominicana, 1979, Medicina Interna e Infectología.

REINGRESO

Rosario Ríos, Edwin, MD - Universidad Central de Madrid, España, 1965, Medicina Física y Rehabilitación. Ejerce en Caguas.

Medicolegal Decisions



NATUROPATH ENJOINED FROM PRACTICING MEDICINE WITHOUT A LICENSE

Evidence amply supported a trial court's findings that a naturopath was engaged in the practice of medicine without a proper license, an Alabama appellate court ruled.

A woman who had been treated previously for cancer was admitted to a hospital for pain in her side. Physicians recommended exploratory surgery, but the patient decided againts it and went to the naturopath's office.

The naturopath took a history from the patient, weighed her, checked her urine and saliva for salt levels, sugar, acidity, and alkalinity, and checked her blood pressure. She allegedly told the patient that she could help her without surgery. She recommended a diet and administered colon therapy, saying that the enemas would wash the poisons out of the patient's body.

After about nine months, the naturopath concluded that her nutritional program was not helping the patient and recommended that she see an osteopath. The osteopath diagnosed cancer of the liver and prescribed something for her to take. The naturopath later testified that she did not try to treat the patient for cancer after the osteopath made the diagnosis. However, there was a prescription for ground-up apricot pits mixed with mashed bananas, in her handwriting. It contained a large dose of laetrile. The patient died a few months later of "apparent heart failure".

The State Medical Licensure Commission petitioned enjoin the naturopath from practicing medicine without a licence. A trial court granted an injunction against practicing medicine without a license, operating a clinic as a medical office, and using the designation "Dr." The naturopath appealed to the Alabama Supreme Court, which transferred the case to the appellate court.

The appellate court found from evidence that the naturopath had not qualified to receive a license as a naturopath and could not be so licensed because the state legislature had not made this a brach of the healing arts.

The court found that the naturopath, in prescribing foods and vitamins and administering colonic irrigations, undertook to treat the patient's pain "by any means or instrumentality," amounting to the practice of medicine under law. She also operated an office for the purpose of performing such acts and used the work "doctor" or "Dr." in referring to herself and in advertisements, also a violation of the law. The court affirmed the trial court's findings.—Williams v. State of Alabama ex rel. Medical Licensure Commission, 453 So.2d 1051 (Ala.Ct. of Civil App., April 11, 1984; cert. denied, Ala. Sup.Ct., July 13, 1984)

VIABLE FETUS IS PERSON, MASS. HIGH COURT RULES

A viable fetus is a person for purposes of the vehicular homicide statute, the highest court of Massachusetts ruled.

A man operating a motor vehicle on a public way struck a pedestrian who was eight and a half months pregnant. The fetus died in the womb and was delivered by cesarean section. Autopsy revealed that the fetus died as a result of internal injuries caused by the impact of the vehicle.

The driver was charged with violating the homicideby-motor-vehicle statute. The case was transferred to the highest state court on the court's own motion. The question before the court was whether a viable fetus was a person under the statute.

The court said that according to approved usage and giving terms their ordinary meaning, the word "person" was synonymous with the term "human being" and that the offspring of human parents could not be considered to be other than a human being and therefore a person. The court also said that a viable fetus could be the victim of a homicide under common law. The court concluded that in enacting the vehicular homicide statute, the legislature contemplated that the term "person" would be construed to include viable fetuses.

The court said that the common law had for many years been that destruction of a fetus in utero was not a homicide because it was difficult to know whether the fetus was alive at the time of injury. The court pointed out that medical science now may provide competent proof as to whether or not a fetus was alive. In the present case, physicians were able to detect a fetal heartbeat after the collision.

In deciding that viable fetuses should be protected under criminal law, the court said that important considerations were the foreseeability to the new rule and the extent to which the driver might have relied on the old rule. The court said that prospective-only application of the decision would avoid the appearance of action that was badly motivated or erratic and ensure impartiality and regularity in decision-making. Concluding that the decision whould not be applied to the driver in this case, the court said that it would be applied to homicides occurring after the date of the present decision. The court sent the case back for further proceedings.— Commonwealth of Massachusetts v. Cass, 467 N.E.2d 1324 (Mass.Sup.Jud.Ct., Aug. 16, 1984)

PATIENT SUES FOR NEGLIGENCE IN PROSTATE RESECTIONS

A trial court erred in finding that a patient's impotence was not due to negligence in performance of prostate resections, a federal appelate court in New York ruled.

The patient had a transurethral resection of the prostate at a VA hospital. Afterward because of failure to cut away a flap of tissue, the patient was unable to void. Eight days later, a second resection was performed. At this operation, the surgeon apparently cut open the patient's urinary sphincter, resulting in total urinary incontinence.

A physician who specialized in anti-incontinence devices implanted a prosthesis after a third resection to remove excessive, scar tissue. Later, an operation was performed to remove more scar tissue, allegedly resulting from the firs two operations. Although the prosthesis worked, the patient continued to drip urine and suffered some discomfort, restricting his activities. He also suffered from impotence.

In a malpractice action under the Federal Tort Claims Act, based on the two operations at the VA hospital, the government conceded that the surgery had been performed negligently and had rendered the patient incontinent. A psychologist who had been treating the patient stated that his psychotic state and impotence were unqualifiedly the result of the operations performed at the VA hospital. The VA surgeon said that impotence was a known complication of such operation. The surgeon who implanted the prosthesis stated that a patient who was incontinent might lose his potency for psychological reasons because he was wet most of time. The trial judge found that the impotence was not due to negligence by the VA surgeon.

On appeal, the court said that the atrial court's finding was not supported by the evidence. At a minimum, the court said, the psychologist's testimony provided the requisite expert testimony. The court found that the trial court's award of \$15,000 for five years of pain and suffering and \$15,000 for future pain and suffering approached being so inadequate as to shock the court's conscience. Reversing the trial court's judgment, the court sent the case back for further proceedings.—Korek v. U.S., 734 F.2d 923 (C.A.2, N.Y., May 11, 1984)

DELAYED TREATMENT OF HAND CONTRIBUTED TO INJURIES

Evidence supported a trial court finding that delay in treatment contributed to injuries to a patient's fingers, a federal appellate court in Puerto Rico ruled.

The patient was taken to a hospital for treatment of injuries to her head and hand, suffered when she raised her hand to protect herself while being struck with a metal rod. X-rays were taken of her head and hand and her head was stitched. However, the only thing done for her hand was to place cotton balls soaked in saline solution on the injuries. More than 21 hours after the injuries and about 18 hours after she arrived at the hospital, the patient's hand was operated on. Dry gangrene later developed in her little finger, which was amputated at another hospital. She also suffered a deformity of her ring finger with stiffness of the joints.

The patient sued the hospital for negligence in delaying treatment of her hand injuries. At the trial, a physician testified that the delay in treatment fairly contributed to the swelling of the patient's fingers and that in approximately 99 per cent of such cases the fingers would have healed successfully. The patient was an airline stewardess before the injuries occurred and returned to her former job only after extensive psychiatric counseling. The jury awarded her \$175,000.

On appeal, the hospital contended that there was no evidence to support a finding that delay in treatment caused or contributed to the patient's injuries. The court said that the patient was not required to show that the injuries were caused solely by the delayed treatment. While the physician could not say that the delay was a more significant factor than others, it was clear that the delay fairly contributed to the injuries and the jury were entitled to make up their own minds.

The court said that the delayed treatment, the nonalignment of the fracture, and the trauma all contributed to the injuries. The delay was attributable to the hospital's negligence, and the jury could also have found the hospital responsible for the improper alignment. The court found this to be sufficient to provide causation. Although there was conflicting testimony, the court found that the verdict was not against the weight of the evidence and affirmed the lower court's judgment.—

Heddinger v. Ashford Memorial Community Hospital, 734
F.2d 81 (C.A.1, Puerto Rico, May 15, 1984)

RADIOLOGIST NOT NEGLIGENT IN READING FRACTURE X-RAYS

A patient's experts failed to present evidence to establish negligence on the part of physicians, a Georgia appellate court ruled.

The patient was treated for an ankle injury at a hospital emergency room. A radiologist concluded from X-rays that there was no fracture. A sprain was diagnosed on X-

rays taken at a clinic six days later. A physician who treated the patient at the clinic found that the X-rays showed no fracture. About a month later, no fracture was found on additional X-rays. The patients was still suffering pain over a month after the injury occurred, and the physician gave him the clinic's X-rays and referred him to an orthopedic specialist. The orthopedist diagnosed an osteochondral fracture of the left talus. A second orthopedist agreed with the diagnosis.

The patient sued the radiologist, the clinic, and the clinic physician. He alleged that the radiologist was negligent in reading and interpreting the X-rays taken on the day of the injury. He contended that the physician had negligently failed to recognize the existence of the fracture and therefore was negligent in treating him.

The physicians moved for summary judgment. They supported their motions with affidavits stating that they had exercised the required degree of care and skill. The patient submitted affidavits of the two orthopedists. The trial court found that he had not introduced sufficient evidence as to whether the physicians had failed to exercise the appropriate degree of skill and care and awarded summary judgment for the physicians.

On appeal, the court pointed out that both orthopedists testified that their ability to see the fracture on the X-rays was based on the fact that they were aware of the patient's history subsequent to the X-ray examination. The second orthopedist admitted that it was possible for a physician exercising the required degree of skill and care to overlook a fracture on an X-ray that could be spotted later by someone who was aware of the history after the X-ray was taken. Neither orthopedist said that the physician's method of treatment for the "sprained" ankle was negligent. The court affirmed the lower court's judgment.—Jones v. Finley, 316 S.E.2d 533 (Ga.Ct. of App., Feb. 27, 1984; rehearing denied, March 9, 1984; cert. denied, Ga.Sup.Ct., April 18, 1984)

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IMMUNE SYSTEM DEFICIENCY RELATED TO DEPRESSION

Decreased lymphocyte function appears to be associated specifically with clinical depression and not to effects of hospitalization or to other psychiatric disorders, according to a study from New York's Mount Sinai School of Medicine. Writing inthe February 1985 Archives of General Psychiatry, Steven J. Schleifer, MD, and colleagues say they compared lymphocyte responses of ambulatory patients with major depressive disorder with those of matched controls. They also compared responses of hospitalized schizophrenic patients with those hospitalized for elective surgery. Study results suggest that "altered immunity in depression may be related to severity of depressive symptoms," they say.

REPORT NEW TECHNIQUE FOR STUDYING KIDNEY FUNCTION

Correction of a dangerous buildup of acid in kidney tissue can be gained by administration of adenosine triphosphate (ATP)-magnesium chloride, according to a new study in the February 1985 Archives of Surgery. Bauer E. Sumpio, MD, PhD, and colleagues from Yale University School of Medicine say they were able to track molecular events in intact living cells and perfused kidneys by using high-resolution phosphate 31-nuclear magnetic resonance spectroscopy. Using animal models, they were able to correct intracellular acidosis within 75 minutes, following blood-flow stoppage and reperfusion. ATP levels increased to 69 percent within ten minutes, they say.

PROMPT ANTIBIOTIC THERAPY BEST STREP THROAT TREATMENT

Early administration of penicillin dramatically relieves the symptoms of streptococcal pharyngitis (strep throat), according to a report in JAMA. The finding challenges the common procedure of obtaining throat culture results before prescribing antibiotics. LTC Marvin S. Krober, MC, USA, of Tripler Army Medical Center, Honolulu, and colleagues say theirs is the first placebo-controlled, double-blind study to show that penicillin not only kills the bacteria and prevents complications but also alters the acute phase of the disease. Forty-four children suspected of having strep throat were given throat cultures and were randomly assigned to receive either penicillin or placebo for 72 hours. Their symptoms were assessed at 24, 48 and 72 hours. Culture results were positive for 26 (54 percent) of the children.

Of these 26, the 11 children who had taken penicillin recovered more quickly than the 15 who had taken placebo. "Significant differences in the presence and degree of fever and severity of symptoms persisted in the placebo-treated group for 48 hours," the researchers say. Those treated with penicillin showed symptomatic improvent, were afebrile within 24 hours, and their throat cultures had become negative. In contrast, the researchers say, those treated with placebo had persistence of fever and other symptoms for 48 hours, and their throat cultures remained positive, so they were considered contagious throughout the 72-hour observation period.

Commenting editiorially, Vincent A. Fulginiti, MD, of the University of Arizona, Tucson, says the report fuels the controversy regarding the management of strep throat. Often penicillin is given only when results of the throat culture are known, usually after a day or two. But Fulginiti notes, "If Krober et al... are correct, then time is critical, especially to the patient who is suffering from the symptoms!"

Fulginiti says many physicians do begin treatment with penicillin before culture results are available, and some question whether cultures are necessary at all. "Coupled with the knowledge that not only do many physicians not use the throat culture to initiate therapy, many of them do not suspend their treatment if the culture is negative." Other physicians, however, have argued that the throat culture is vital, especially for children and teenagers who may be at risk of developing rheumatic fever as a complication.

Fulginiti concludes that accurate diagnosis of strep throat depends on symptoms and culture results. He says physicians should be more liberal in prescribing penicillin for relief of symptoms, but that they should also obtain throat cultures and discontinue therapy when the results are negative.

JAMA March 1, 1985

STUDY CONFIRMS INFLUENZA VACCINE BENEFITS ELDERLY

Influenza vaccine can prevent or reduce the severity of influenza virus infections among the elderly or chronically ill, according to a study in JAMA. The data showed that vaccination was associated with a 79 percent reduction in mortality overall.

Peter A. Patriarca, MD, of the Centers for Disease

Control, Atlanta, and colleagues studied the incidence of influenza-like illness smong nursing home residents in Genesee County, Mich., from December 1982 to March 1983. The study included 1,476 residents of 13 nursing homes, 887 of whom had been vaccinated during the previous fall. Residents in homes where outbreaks occurred were studied separately, but there were 329 total cases of influenza-like illness.

"Unvaccinated residents had higher attack rates than vaccinated residents in six of the seven homes with outbreaks and were more than twice as likely to develop influenza-like illness overall," the researchers say. They add that overall attack rates were also higher for unvaccinated resident in the six homes with no outbreaks.

"Influenza vaccine also appeared to reduce the risk of pneumonia and death even when it failed to prevent influenza-like illness," the researchers note. Twenty-six (17 percent) of 150 vaccinated cases developed pneumonia and eight (5 percent) died, whereas 47 (27 percent) of 175 unvaccinated cases developed pneumonia and 25 (14 percent) died.

Overall vaccine efficacy was approximately 37 percent in the nursing homes where outbreaks occurred and about 28 percent in the others. The researchers conclude that although the vaccine may not provide optimal protection against the virus infections, it may weaken it and save lives. "Compared with vaccinated persons, unvaccinated persons were more likely to be hospitalized, develop pneumonia, and/or die of influenza-like illness," they say.

JAMA Feb. 22, 1985

COMMON HEART DRUG CAN CAUSE HEART SYMPTOMS

The most commonly used heart drug paradoxically can produce a decrease in blood pressure and blood flow to the heart, and an increase in angina, according to a new study from Brown University in Providence, R.I., that appears in JAMA.

William E. Boden, MD, and colleagues report that the symptoms were recorded with ten patients following combined nitrate/beta blocker/nifedipine therapy. The heart patients had reported angina within 20 to 30 minutes of nifedipine ingestion and subsequently were studied before and after usual drug use.

"Mean systolic blood pressure fell from 109 to 94 mm Hg after nifedipine; mean heart rate increased from 64 to 68 beats per minute, seven patients developed transient ECG changes during the hypotensive period," the researchers report. Medication was changed to diltiazem hydrochloride with six patients and nifedipine dosage was decreased from 92 mg per day to 62.5 with the remaining four patients. All experienced clinical improvement.

The data suggest that nifedipine administration in daily doses of 80 mg or more may result in symptomatic hypotension, angina pectoris and reversible myocardial

ischemia in certain patients with "medically refractory angina pectoris," the researchers say. The symtoms presumably are due to fall in coronary blood flow resulting from a narrowing of the coronary artery complicated by the fall in blood pressure.

"In summary, we believe that nifedipine should be used with caution in patients with refractory angina pectoris who are prone to arterial hypotension, particularly if they are receiving concomitant beta-adrenergic blocker and/or nitrate therapy," they say. "Reduction in the daily nifedipine dose, or changing to an alternate calcium-channel blocker with less pronounced arteriolar dilating properties (e.g., diltiazem hydrochoride) may result in clinical improvement."

JAMA Feb. 22, 1985

BLOOD TEST DETECTS AIDS VIRUS ANTIBODIES

A blood test that detects antibodies to HTLV-III, the virus causally implicated in acquired immune deficiency syndrome (AIDS), has been proved highly specific and sensitive. The finding is reported in the Journal of the American Medical Association. The test will be useful in screening blood donors and populations at risk for AIDS, and will help in defining the spectrum of diseases that are etiologically related to HTLV-III.

Stanley H. Weiss, MD, of the National Cancer Institute, Bethesda, and colleagues used the semiautomated test on blood samples from 88 patients with AIDS and 297 healthy persons. They found that 72 (82 percent) of 88 patients with AIDS were positive for antibody, 14 (16 percent) were borderline, and two (2 percent) were negative. "In contrast, only I percent of 297 volunteer blood donors were positive, 6 percent were bordeline, and 93 percent were negative," the researchers say. Current precautions for health care employes appear to be adquate, since none of the 188 laboratory and health care workers tested had positive results.

The incidence of AIDS in selected populations is reviewed in another report by Ann M. Hardy, DrPH, and colleagues of the Centers for Disease Control in Atlanta. Incidence rates were estimated for a 12-month period (June 1, 1983 to May 31, 1984) for single men, intravenous drug users, Haitians living in the United States, persons with hemophilia A and B, female sexual contacts of male IV drug users, and blood transfusion recipients.

"Single men in a San Francisco and Manhattan, IV drug users in New York City and New Jersey, hemophilia A patients, and recent Haitian entrants had the highest rates of disease (82.0 to 268.9 per 100,000)," the researchers say. "Although blood transfusion recipients and female sexual contacts of male IV drug users had much lower average yearly rates than did persons in the four other groups (0.4 to 9.4 per 100,000), they still had a higher incidence rate of AIDS than did persons not belonging to any of these groups (0.1 per 100,000)."

Commenting editorially, Thomas C. Quinn, MD, of

the National Institutes of Health, observes that homosexual or bisexual men, intravenous drug users, Haitians who have immigrated to the United States since 1978 and hemophiliacs constitute 94 percent of AIDS cases in this country. He adds, "With an incubation period of approximately two years and a prevalence rate of HTLV-III infection of over 80 percent in selected high risk groups...we can anticipate a continued exponential increase in the incidence of AIDS."

Quinn says although there is a test to determine the presence of antibody to HTLV-III, confirmatory assays are needed. He notes that only a small percentage of persons infected with the virus develp AIDS, and there is evidence of an asymtomatic carrier state. "It is hoped that prospective studies on the natural history of AIDS using serological and virologic markers of HTLV-III will determine which factors are responsibble for the host response to infection," he says.

JAMA Jan. 11, 1985

CARE DELAYED FOR SOME DOWN'S SYNDROME INFANTS

Some children with Down's syndrome are being denied standard cardiac care by the process of late referral, according to a study in the January American Journal of Diseases of Children. Henry M. Sondheimer, MD, and colleagues from the State University of New York-Upstate Medical Center in Syracuse reviewed 36 patients with complete atrioventricular canal defect, and found that eight without Down's syndrome were referred before one year of age. Of the 28 with Down's syndrome, 18 were referred before one year, and 10 after one year. Of those 10, half were inoperable because their defect had progressed to pulmonary vascular obstructive disease. "Some of our patients with late referral were initially evaluated elsewhere," the researchers say. "We question if the parents of these children were being allowed the opportunity to make an appropriate decision. However, our data do not permit firm conclusions but do suggest that late referral is an incorrect choice medically."

ADOLESCENT DELINQUENTS HAVE MEDICAL, LEARNING DEFICITS

Youngsters betweem the ages of 11 and 16 convicted of crimes are more likely to have reported medical problems, developmental language disabilities, as well as socioeconomic deficits, according to a report from The Children's Hospital in Boston. Writing in the January American Journal of Diseases of Children, Melvin D. Levine, MD, and colleagues report on a study of 53 delinquents and a like number of matched control youngsters. Among noted medical problems of delinquents: three times the number of perinatal problems and conspicuous occurrence of head trauma serious enough to require medical treatment. Academic delays oof

significant degree among delinquents also were found. Most additionally came from broken families. "It can be argued that a child who is disadvantaged only socioeconomically, only medically, or only neuro-developmentally possesses sufficient resiliency to avoid the devastating outcome of delinquency," the researchers say. "A youngster who has endured poverty, recurring health problems, and inordinate educational failure may be vulnerable to delinquency even within a stable family," they conclude.

ANXIOUS MOTHERS HAVE 'COLICKY' BABIES

Neither the method of feeding nor the type of milk fed accounts for "colicky" babies, according to a report from pediatricians at Yale University School of Medicine. The problem more likely is related to parental anxiety, say Brian W. C. Forsyth, MB, ChB, and colleagues writing in the March American Journal of Diseases of Children. They followed 189 mothers intending to breast feed and 184 intending to formula feed their infants for a four-month period. In each group, breast or bottle, 35 percent of mothers reported feedings problems. The researchers advise pediatricians to watch for signs of anxiety concerning feeding on the part of mothers. Counseling and reassurance can mitigate the problem, they say.

ASBESTOS FOUND IN INFANT LUNGS

Long associated with occupational or environmental exposure, asbestos now has been found in infants less than ten months of age, according to a report in the March Archives of Pathology and Laboratory Medicine. Abida K. Haque, MD, and colleagues from the University of Texas Medical Branch in Galveston conducted systematic examinations of 17 infants and found asbestos bodies in the lung tissue of six. Exposure may have been from asbestos sprayed on ceilings, asbestos from incubator gaskets, or from other sources in home or hospital. Concentrations were comparable with those found in some adult lung cancer patients, the researchers say. They plan further studies to determine the presence and extent of asbestos in infant lungs.

ALL CONTACT LENSES HAVE PROTEIN DEPOSITS

All soft contact lenses have protein adherent to their surface as a result of normal wear, according to a new study in the February 1985 Archives of Ophthalmology. The surface deposits are capable of decreasing the life of a lens, causing discomfort and contributing to blurred image. Olafur G. Gudmundsson, MD, of Harward Medical School, and colleagues examined worn soft contact lenses from five asymtomatic subjects by immunofluorescence microscopy for type of protein on the lens surface. They found lysozyme, IgA, lactoferrin, and IgG. "New, never-worn soft contact lenses did not stain for any of the proteins examined in this study," the researchers report.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interes general para la profesión médica

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito. El articulo, si se aceptara, será con la condición de quese publicará únicamente

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Articulos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés),

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Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre parentesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

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Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas cientificas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

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The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

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Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially).

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

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References: 1. Kales J et al: Clin Pharmacol Ther 12:691-697, Jul-Aug 1971. 2. Kales A et al: Clin Pharmacol Ther 18:356-363. Sep 1975. 3. Kales A et al: Clin Pharmacol Ther.19:576-583, May 1976. 4. Kales A et al: Clin Pharmacol Ther.39:76-583, May 1976. 4. Kales A et al: Clin Pharmacol Ther 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: J Am Geriatr Soc 27:541-546, Dec 1979. 6. Kales A, Kales JD: J Clin Pharmacol 3:140-150, Apr 1983. 7. Greenblatt DJ, Allen MD, Shader RI: Clin Pharmacol Ther 21:355-361, Mar 1977. 8. Zimmerman AM: Curr Ther Res 13:18-22, Jan 1971. 9. Amrein R et al: Drugs Exp Clin Res 9(1):85-99, 1983. 10. Monti JM: Methods Find Exp Clin Pharmacol 3:303-326, May 1981. 11. Greenblatt DJ et al: Sleep 5(Suppl 1):S18-S27, 1982. 12. Kales A et al: Pharmacology 26:121-137, 1983.

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evaluation.

ContraIndications: Known hypersensitivity to flurazepam HCI; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/ or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, Gl pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect.

Dosage: Individualize for maximum beneficial effect. Adults: 30 mg usual dosage; 15 mg may suffice in some patients. Elderly or debilitated patients: 15 mg recommended initially until response is determined.

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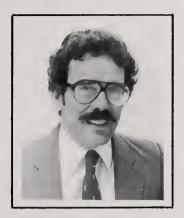
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partir del número pasado, correspondiente al mes de abril de 1985, la circulación del Boletín de la Asociación Médica de Puerto Rico se aumentó a 3,000 ejemplares mensuales. Este aumento era una de las metas a largo plazo que se autoimpuso la Junta Editora a Principios del año 1982. Como prerequisito para ello se debía mejorar la calidad científica y gráfica, poner la revista al día y sobretodo hacerla autosuficiente. Logrados estos objetivos se hizo posible aumentar la circulación de nuestra revista científica. Con ese recurso adicional se decidió enviar mensualmente el Boletín a todos los médicos en adiestramiento en Puerto Rico libre de costo para ellos. Esta acción de la Asociación Médica de Puerto Rico deja claramente establecida la seria intención de colaborar activamente en la formación profesional de la clase médica nacional y ampliar más aún los servicios que les ofrece. Sin embargo, la cantidad de Internos y Residentes en las instituciones de enseñanza médica en Puerto Rico sobrepasa la cantidad disponible para hacerle llegar un número a cada uno de ellos. Es por ello que lo enviaremos mesualmente de forma rotativa entre las instituciones acreditadas. Confiamos que para 1986 sea posible volver a aumentar la circulación, de manera que el Boletín sea recibido mensualmente por todos estos jóvenes médicos puertorriqueños en una etapa tan importante de su vida como lo son esos primeros años de estudio y trabajo. A todos ellos les dejamos saber que la Asociación Médica de Puerto Rico también vela por ustedes y no cesará en su empeño de servirles, aligual que a toda la clase médica, aún a expensas de grandes sacrificios individuales y colectivos.

Milanimie Suo

Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico

BOLETIN



VOL 77/NUM 5 MAYC 1985

NUESTRA PORTADA

Sillón-Oleo sobre lino del Artista puertorriqueño Jorge Rechany

Nació en San Juan, el 22 de abril de 1914. Estudió con el pintor Ramón Frade (1927) y con el maestro Sánchez Felipe (1930). Ingresa en la National Academy of Design, Nueva York, y realiza estudios bajo la dirección de Olinsky, Dickinson, Anderson y Curry. En 1958 es becado por el Instituto de Cultura para estudiar en la Escuela de Escultura y Pintura, de México, y en el Centro Superior de Artes Plásticas ((INBA), de dicha ciudad azteca. También estudió en 1961 en los talleres E. Pandolini, Pietrasanta, Italia, y en 1974 en el Pratt Graphic Center de Nueva York.

Importantes obras suyas (murales y óleos) se encuentran en: la Rotonda del Capitolio de San Juan, Palacio de la Fortaleza, Museo de Ponce, Palacio Presidencial de Santo Domingo; Universidad de Puerto Rico, Escuela Libre de Música, Instituto de Cultura, Centro Superior de Artes Plásticas, de México; Escuela Pública de Barceloneta; Escuela "Bolívar Pagán"; Instituto de Lexicografía; y Escuela Intermedia de Naguabo. Su obra gráfica está representada en: The British Museum, Londres; Museo de Arte Moderno, de Nueva York; Ibero Club, Bonn; Museo de Arte Moderno, Barcelona; Deutsches Plakat Museum, Esen; Biblioteca Nacional, México; Biblioteca Nacional, de París; Museo de Arte Moderno, Madrid; Museo Vaticano de Arte Sacro Moderno, Roma; Kestner Museum, Hannover; y Museo Real de Bellas Artes, Bruselas.

Entre sus pricipales exposiciones individuales están las de: Galería D'Arte de San Marco, Roma (1962); Ateneo Puertorriqueño; Museo de la Universidad (1963); Instituto de Cultura (1969); La Casa del Arte (1971); Unión Panamericana, de Washington (1973); UPR Recinto Mayagüez (1975), habiendo participado en la 111 Bienal Hispanoamericana, de Barcelona (1955); I Bienal de México (1958), Latin American Art, Buenos Aires; "Once Pintores Puertorriqueños" (UNESCO) Bonn, Alemania (1973); "Dos Siglos de Pintura Puertorriqueña", Casa de Campeche, y las tres bienales de San Juan de Grabado Latinoamericano.

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Bronchodilator

Please see following page for brief summary of the prescribing information, including warnings, precautions, and adverse reactions.

References

^{**}When administered by IPPB

[†]In repetitive-dosing studies with Alupent Tablets and Alupent MDI, the duration of their effectiveness tended to diminish with time. Present studies are inadequate to explain the divergence in duration of efficacy between single and repetitive dosing.

Reilly, EB et al. A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. Curr Ther Res 1974; 16: No. 8, 759-764.

^{2.} Data on file at Boehringer Ingelheim Ltd.

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Contraindications: Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated

Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol

Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed

Pregnancy: Teratogenic Effects: Pregnancy Category C. Alupent, brand of metaproterenol sulfate, has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose, the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose and 31 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent, brand of metaproterenol sulfate, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste

Overdosage: The symptoms of overdosage are those of excessive beta adrenergic stimulation listed under Adverse Reactions. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration

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EDITORIAL

The Logic of a Health System

In Puerto Rico, today more than ever, the health challenge calls for a holistic approach and understanding of the organization of services. The idea is to provide a practical framework for managing relationships between parts that must be coordinated in order to accomplish a set of specific and diverse goals, including the components of the systems; the scarce resources, technologies, and the type of management such system uses; and the prominent sociopolitical elements in its environment.

Health Services, in a macro-social sense, implies a particular system's optic and a continuous process of reviewing pluralistic objectives, designing alternative methods of achieving them, and weighing the effectiveness and costs of the alternatives, largerly in social and economic terms. An institutional rule seems to be here fundamental. What benefits the whole (the system) does not necessarily benefits equally the parts (Medical Center or the University of Puerto Rico Hospital, among others). In other words, the logic of the whole system is something more and complex than the sum of its parts.

When dealing with the University of Puerto Rico Hospital, the Medical Center or even the Department of Health we have to approach these organizations and their problems within the logic of a health system. Such institutional logic challenges the orthodox maxim of management, administration and arragement which takes the reliability of a health system to depend upon the perfectability (or liberation as oppose to captive) of one of its

parts or components.

The question is not to build a truly University Hospital, totally independent from the Medical Center, but to ponder if it is possible to design and satisfactorily manage a health system that is more effective, adaptive and socially relevant, than any of its components. The Puerto Rican experience shows that the answer is yes! This has been done by creating a network of unit and institutions of parallel and coordinated linkages which provide organizational options so that if transfer is not effected at one point, it can be had at others. Such organizational logic is that one way to increase the capability of the institutional system is by way of coordination. The implementation of this management rule rest upon a theorem which states the probability of success for a system increases exponentially as the number of units work jointly towards diverse sets of social goals and objectives.

One can not put aside the reality that health policy making, within an heterogeneous domain, sets for huge of bargaining and constructive competition involving the participation of different groups, units and organizations often with conflicting points of view. The system is not constituted by angels, but by men and women wishing to confront not a routine to be administered in isolation, but health problems to be solved.

The task is one of organizational design maintenance. This perspective takes the production of a collective output as a critical problem. The structure of the complex system should be used to enhance the system's capability and productibity. A prime implication is that we should reinforced an arrangement aiming at facilitating positive contributions of the interrelated units to the whole. This is also the logic of public service...! Such a strategy represents a formidable effort to confront a double problem: increasing the quality of medical care and reducing the costs of such endeavors to allow social access.

For physicians and other related professions this is an organizational problem which requires the utilization of knowledge not given to anyone in its totality. It also suggests that there is something fundamentally wrong with an approach that disregards other essential parts of the system with which we have to deal.

Rafael Burgos Calderón, M.D.

Past Executive Director

Jest Zunga

Puerto Rico Medical Service Administration

Puerto Rico Medical Center

ESTUDIOS CLINICOS

Serum Phosphate Levels in Acute Myocardial Infarction

Héctor García, M.D. Edgardo Hernández, M.D., F.A.C.C. María E. Alvarez, M.D. Juan M. Aranda, M.D., F.A.C.C.

Hypophosphatemia is a common finding in hospitalized patients. Gilbert¹ reported an incidence of 21.6% among patients hospitalized in a general medicine ward. Intravenous administration of dextrose in water, diuretics, hyperalimentation and alcohol intake are the etiological factors most frequently encountered.²⁻³ Functional abnormalities of the red cells, leukocytes and platelets as well as CNS dysfunction and rhabdomyolosis are some of the reported complications of hypophosphatemia.²⁻⁴

In 1982, Gould et al⁵ reported a decline in serum phosphate in patients with an acute myocardial infarction. This observation was confirmed by Yaroslavsky.⁵ However none of these clinical reports addressed the issue of the clinical significance of this finding.

The purpose of this study is to document the occurrence of hypophosphatemia in acute myocardial infarction and to assess its clinical significance in regard to the patients clinical course and outcome.

Material and Methods

A retrospective review of the medical records of all patients admitted to the coronary care unit of the San Juan VA Hospital during the period of September to December of 1982 was performed. The patients were classified as having an acute transmural myocardial infarction if they presented the classic electrocardiographic changes (appearance of new Q waves greater than 0.03 seconds) with the corresponding enzymatic elevation within the clinical setting of an ischemic event. Patients who had ST-T wave changes (ST depression and/or T wave inversion) without pathologic (greater than 0.03 seconds) Q waves were classified as having a non-transmural myocardial infarction if they fulfilled the enzymatic and clinical criteria previously mentioned. Patients who did not fulfill these criteria were included in the non myocardial infarction group. Patients with malnutrition, alcoholism, diabetes mellitus or receiving antacids or calcium binders were identified. Those with

renal insufficiency (creatinine > 1.5 mg%) were excluded. Admission laboratory tests were recorded for the first days. Significant cardiovascular complications were noted and classified as electrical (ventricular arrhythmias or heart block) or mechanical (congestive heart failure or cardiogenic shock). Serum phosphate (P) determination was performed according to the method reported by Drewes in a commercially available automatic clinical analyzer. Normal values are 2.5 to 4.9 mg/dl. A control group was defined as sex-age matched patients admitted to the coronary care unit during the same period of time and found not to have an acute myocardial infarction. Statistical analysis was performed using the unpaired student t-test. Chi square determination was used to compare percentage differences between the groups. P values less than 0.05 were considered statistically significant (two-tailed).

Results

A total of 75 patients who fulfilled the entry criteria were analyzed. Twenty-eight (28) were found to have an acute myocardial infarction (group A) and 47 did not (group B). All 75 patients were males and the mean age was similar in both groups (table I). When comparing the risk factors for hypophosphatemia between the two groups, we found no statistical difference in the prevalence of diabetes mellitus, alcoholism, use of diuretics. administration of glucose intravenously or the use of antacids (table I). The mean serum phosphate was lower in the myocardial infarction group (group A) on days 1, 2 and 3 than in the non-infarction group (group B). The lowest value of serum phosphate occurred on day 3 in both groups (table II). There were 8 patients (29%) in group A versus 3 (6%) patients in group B with one or more low serum phosphate determination during the first three days of hospitalization. The prevalence of factors associated with hypophosphatemia was not different in the hypo and normophosphatemic group A patients. The incidence of electrical events was higher in the hypophosphatemic group A patients than those with normal phosphate determination (75% vs 50%), however this difference did not reach statistical significance (table III).

From the Cardiology Section, Veterans Administration Hospital and the University of Puerto Rico, School of Medicine, San Juan, Puerto Rico

TABLE I

Clinical Characteristics of 75 Patients Admitted to the

CCU from September to December 1982					
	Group A N=28	Group B N=47	Р		
Age	59±7	61±5	NS		
Diabetes Mellitus	8(29%)	12(26%)	NS		
Alcoholism	4(15%)	7(15%)	NS		
Diuretics	14(58%)	27(57%)	NS		
Antacids	2(7%)	11(23%)	NS		
IV. D, W	23(82%)	32(68%)	NS		

TABLE II

Mean Serum Phosphate Determination in the Myocardial and Non Myocardial Infarction Group

	Group A	Group B	P
Mean Serum P	N=28	N=47	
Day 1	3.0±.6	3.4±.5	<.05
Day 2	3.2±.4	3.8±.3	< .05
Day 3	2.4±.2	3.0±.5	< .05

TABLE III

Serum Phosphate Determination in the Myocardial Infarction Group

	Hypophosphastemic N=8	Normophosphatemic N=20	Р.
Mechanical events	4 (50%)	11 (55%)	NS
Electrical events	7 (88%)	10 (50%)	NS
Infarct location			
Anterior	7 (88%)	10 (50%)	NS
Inferior	1 (12%)	10 (50%)	NS

Discussion

Gould et al⁵ reported the occurrence of a decline in serum phosphate in patients with acute myocardial infarction. This finding was confirmed by Yaroslavsky et al.⁶ However, none of the mean serum phosphate values reported by these authors were in the hypophosphatemic range. Our findings confirm the works of Gould and Yaroslavsky but differ from their findings in that 29% of our patients with acute myocardial infarction developed hypophosphatemia.

Various speculations as to the cause of the decline in serum phosphate have been made. An increase in PTH secretion with a decline in the tubular reabsortion has been proposed as a possible mechanism.⁴ However, Yaroslavsky⁶ demonstrated that there was no variation in serum PTH levels during the period of decline of serum phosphate when compared to a control group. Changes in tubular reabsortion or phosphate excretion were not detected in his series.

An alternative explanation for the fall in serum phosphate is a shift from extracellular to the intracellular

compartment.⁸⁻⁹ Opie, ¹⁰⁻¹¹ produced experimental myocardial infarction in baboons and demonstrated an increase in phosphate content throughout the myocardium. This shift of phosphate my be secondary to increased glycolitic activity.

There were 8 patients with one or more low phosphate determination in the myocardial infarction group. As previously reported by Gould et al,⁵ this usually occurred in the third day of hospitalization. Although depression of myocardial contractility may occur in the presence of hypophosphatemia, it is usually seen after chronic depletion of phosphate stores.⁸ The prevalence of mechanical events (congestive heart failure or cardiogenic shock) was not significantly different in the hypophosphatemic myocardial infarction patients.

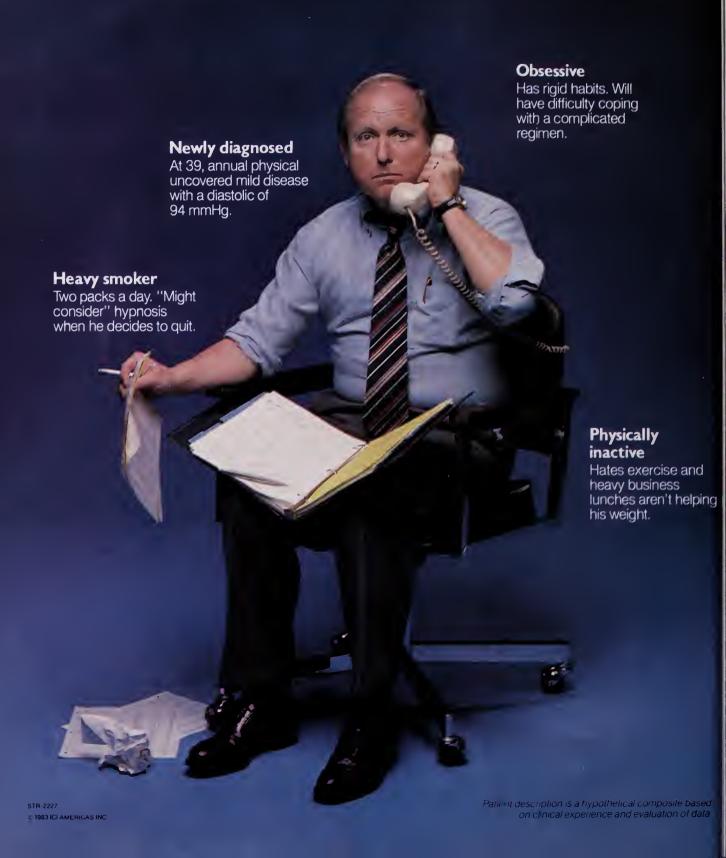
We found a tendency toward a higher frecuency of electrical events in hypophosphatemic group A patients although, this difference did not reach statistical significance. Lichtman and his group³ demonstrated that hypophosphatemia causes a decrease in 2, 3-DPG in red blood cells. Decreased levels of 2, 3-DPG is associated with an increase in the affinity of hemoglobin for oxygen. This may worsen tissue hypoxia and facilitate the emergence of an arrhythmogenic foci.

The etiological factors associated with the development of hypophospatemia in patients with an acute myocardial infarction have not been clearly identified. The clinical significance of this findings is still controversial. A large prospective study is needed to clarify the incidence and clinical significance of this finding in patients with an acute myocardial infarction.

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What can you do for hypertensives like Paul H?



Rely on one-tablet-a-day dosage and cardioselectivity.

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Paul H represents 2,514 men under 40 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

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The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Paul H's age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Reasons for this are not fully understood, but smoking has been implicated especially in males like Paul H. TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Paul H...and virtually all your hypertensive patients

TENORMIN® (atendal)



and virtually all your hypertensive patients TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-{2'-hydroxy-3'-{1-methylethyl} amino} propoxy}. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

thiazide-type durent.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further.

WARNINGS: Cardiac Fallure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and duretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction. In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac taifure. At the tirst sign or symptom of impending cardiac failure, patients should be fully digitalized and /or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Foffowing abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to firmit physical activity to a minimum. TENORMIN should be reinstated if windrawal symptoms occur.

Bronchospasite Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta,-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the do

Increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the fast dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichforcethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (e.g. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as disziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked brady-cardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

of cloridine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacilation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenoid (starting at 15 mg/kg/day or 7 5 times the maximum recommends human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenoid/kg/day (150 and 75 times the maximum recommended human dose,

USAGE IN PREGNANCY: Pregnancy Category C Atenolol has been shown to produce a dose related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kgg 25 or more times the maximum recommended human dose. Although similar effects were not se in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and welf-controlled studies in pre nant women. TENORMIN should be used during pregnancy only if the potential benefit justifiest potential risk to the tetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receivin

atenolol

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimat
were derived from controlled studies in which adverse reactions were either volunteered by the
patient (U.S. studies) or elicited (eg. by checklist—toreign studies). The reported trequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when
these reactions were volunteered. Where frequency of adverse effects for TENORMIN and place

semilar equilar leaf topic procedure. is similar, causal relationship is uncertain.

these reactions were volunteered. Where frequency of adverse effects for TENORMIN and place is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages, first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headeness (1%-0.9%), triedness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0.9%), depression (0.6%-0.5%), freaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0.9%), nausea (4%-1%)

RESPIRATORY (See WARNINIOS) wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headeness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

MESCELLANEOUS. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy approximate proprise of skin rashes and/or dry eyes associated with the test of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be clos

TENORMIN (atenolo). Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress. Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by discrientation of time arplace, short-term memory loss, emotional lability with slightly clouded sensorium, decreased promance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon. Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practold has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

reaction

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific informatio on emergency treatment of overdosage is available. The most common effects expected with ove dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotensio bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or no epinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Amnophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose.

Bronchospasm: Aminophylline, isoproterenol, or atropine Hypoglycemia: intravenous glucose DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit. TENORMIN may be used alone or concornitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs unit creatinine clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1 73 m²)	Atenolol Elimination Half-lite (hrs)	Maximum Dosage
15-35 <15	16-27 >27	50 mg daily 50 mg every other d
		Alexandra, dal bandana condes

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. **HOW SUPPLIED:** Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets wit Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 talets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 10 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled rootemperature.

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Seminario de Infectología

Botulismo Infantil

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Resumen: El síndrome de botulismo infantil es una entidad infecciosa causada por la ingestión de las esporas de *Clostridium botulinum*. Una vez en los intestinos, estas esporas germinan y producen las toxinas responsables del cuadro clínico. El síndrome afecta a los niños mayores de 22 días y menores de 13 semanas. El cuadro clínico se caracteriza por estreñimiento y debilidad general lo cual puede progresar a fallo respiratorio en casos severos.

El tratamiento de estos pacientes consiste en medidas de sostén. Muchos recomiendan una traqueostomía temprana y ventilación para prevenir una muerte súbita secundaria a fallo respiratorio.

Hasta el 1976 se conocían dos formas de presentación clínica de botulismo. La forma mejor conocida se transmite por alimentos inadecuadamente preservados y contaminados con la toxina de Clostridium botulinum. La otra forma de presentación clínica ocurre luego de una herida en la cual el organismo infecta y produce la toxina en el tejido traumatizado.

En el 1976, Pickett reporta su experiencia en dos casos clínicos² y describe el botulismo infantil como una nueva entidad clínica. Establece que el botulismo infantil, contrario al botulismo clásico, es el resultado de la producción de la toxina de C. botulinum in vivo, luego de que las esporas del microorganismo germinan en el lumen del tracto gastrointestinal. El diagnóstico se establece mediante la correlación de la presentación clínica con la identificación del organismo y la toxina en las heces de los infantes afectados.

Desde el reconocimiento de esta nueva entidad clínica han surgido muchas interrogantes que han estimulado el desarrollo de nuevas investigaciones. Ha preocupado a los investigadores el por qué la condición está restringida a un grupo de edad específico, qué rol juega la flora intestinal, qué relación hay con la capacidad inmunológica del infante, qué importancia tiene la dieta del infante y qué relación existe, si alguna, con el síndrome de muerte súbita infantil.

Revisaremos el tema y se discutirán algunas de estas interrogantes.

Epidemiología

Biología del Clostridium botulinum. Clostridium botulinum es un bacilo anaeróbico gram-positivo que puede clasificarse serológicamente de acuerdo a la toxina que produce. Estas toxinas han sido designadas por las letras de la A a la G.1 Los tipos A y B han sido mayormente implicados en la forma infantil de botulismo, aunque hasta el 1982, por lo menos 3 casos de botulismo infantil tipo F han sido reportados.³, ⁴, ⁵ Estos organismos viven en el suelo y producen esporas que son resistentes al calor, la luz y la disecación. La germinación de estas esporas se ha estudiado intensamente in vitro por su relación con el botulismo clásico. Se sabe que en un pH de 5 a 9 con la presencia de alanina o cisteina y a una temperatura de 4°C hasta 70°C germinan muy bien. Luego de la germinación se requiere un pH neutral y la presencia de aminoácidos y vitaminas para la producción de la toxina. Estas condiciones se dan en el intestino delgado. La toxina que se produce es una molécula de dos subunidades con un peso de alrededor de 100,000. Es la sustancia más venenosa que se conoce, con una dosis letal estimada en 10⁻⁹mg por kilo de peso.

Incidencia y distribución. El botulismo infantil tiene una gran distribución. Se han reportado casos de Australia, Inglaterra y todo Estados Unidos.⁷⁻⁹ La verdadera incidencia y extensión no se conoce con certeza, pero debemos suponer que potencialmente ocurre en todo el mundo, ya que las esporas están distribuidas por todo el planeta.¹ En Estados Unidos la distribución de los casos por el tipo de toxina producida correlaciona con la distribución en el terreno del mismo tipo de C. botulinum previamente identificado.^{10, 11} Los casos causados por la toxina tipo B predominan al este del río Missisippi y los casos del tipo A predominan al oeste del río Missisippi.

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Factores geográficos y climatológicos se han implicado también en la distribución de esta condición. En estudios recientes se ha observado que en una serie de 12 infantes afectados, 11 de éstos vivian en áreas de construcción o donde se había manipulado un suelo alcalino. En cuanto al clima, se ha observado que en Utah los casos reportados en el 1978 ocurrieron entre los meses de marzo a octubre. La mayor cantidad de casos se reportaron en el Area Metropolitana de Salt Lake City, que a su vez recibió una cantidad excepcional de lluvia ese año. 12 Esto sugiere que la alta humedad favorece el crecimiento del organismo en el suelo y que el lodo lo hace más disponible para el transporte en los zapatos.

La incidencia del botulismo infantil en Estados Unidos varía de acuerdo al estado estudiado. Se han reconocido casos de botulismo infantil en 21 de los 50 estados y la mayor incidencia anual de la nación proviene del estado de Utah si ésta se ajusta a la tasa de nacimientos (3 casos por cada 10,000 nacimientos). Sin embargo, el número de casos reportados es mayor en el estado de California.¹²

En el 1978 se reportaron un total de 108 casos en Estados Unidos. Para el 1979 sólo se reportaron 69 casos.

Factores en el huésped. De los casos reportados entre el 1976 al 1979 la edad media era de 13 semanas, sin que se fijara una diferencia significativa por sexo. 13 La característica más sobresaliente observada en el botulismo infantil fue la restricción a un grupo de edad específico. De los estudios realizados por Richard O. Johnson, 14 ningún niño en los que identificó el síndrome era menor de 22 días ni mayor de 246 días. Este patrón también se repetía en otros estudios clínicos y experimentales. 15, 16 Si sabemos que la distribución de las esporas es universal y que hay igualdad de exposición, se debe entonces postular la existencia de factores particulares en este grupo de edad específico que juega un papel central en la patogénesis. Estos mismos factores posiblemente explicarían el hecho de que exista un espectro amplio en la presentación clínica de la condición que fluctúa desde pacientes portadores asintomáticos hasta posiblemente casos de muerte infantil súbita.16, 17 Se han citado factores como la dieta del paciente, la flora y la permeabilidad intestinal, las secreciones gástricas e inmadurez del sistema inmune como algunos de los posibles factores determinantes de la presentación del cuadro clínico en el infante.16

Este fenómeno de restricción de edad también se observó en experimentos con animales. ¹⁵ Al alimentar ratones intragástricamente con esporas de *C. botulinum*, la toxina sólo se recuperaba de la excreta de ratoncitos entre las edades de 7 a 13 días, nunca antes ni después. ¹⁵ Sin embargo, se han reportado dos casos típicos de botulismo tipo infantil en adultos. ¹⁶ En California se describió un caso en el cual la toxina se recobró de un paciente que tenía un tracto gastrointestinal alterado a causa de una enteritis regional. Este paciente había estado sometido a tratamiento con múltiples antibióticos. El otro caso era de un paciente sin diagnóstico de botulismo clásico que desarrolló el síndrome típico de botulismo infantil después de cirugía extensa del intestino. De éste se recobró la toxina y el organismo. ¹⁶

Se sabe que la flora intestinal normal juega un papel importante en el mantenimiento de la homeostasis del tracto gastrointestinal. La flora intestinal puede proteger y prevenir daños por patógenos oportunistas. Aunque no existe evidencia directa que respalde que este fenómeno ocurre en los casos de *C. botulinum*, existe alguna evidencia indirecta que sugiere que la flora intestinal del niño juega un papel determinante en la enfermedad. Se conoce que la flora intestinal en los niños alimentados con leche materna es distinta si se compara a la flora de los niños alimentos con leche sintética. En la primera predomina el *Bacteroides bifidus*, el cual no está presente en los infantes alimentados con leche de vaca. En estos últimos niños, predominan el *Clostridium* spp. y otros bacteroides. 18

Por otro lado se sabe que el desarrollo fisiológico y anatómico del tracto gastrointestinal del infante es incompleto. El desarrollo óptimo de la mucosa luminal para evitar la entrada de antígenos macromoleculares es óptima a los seis meses.¹⁹

Aspectos dietéticos. El Departamento de Salud en California examinó cientos de artículos de la dieta de los infantes afectados en busca de la presencia de C. botulinum o su toxina. Entre otros se examinaron muestras de leche materna, fórmula, cereales, miel, etc. 20-23

El alimento en el cual se identificó el organismo pero no la toxina fue la miel. Se aisló de cinco especímenes de tres diferentes fabricantes. Al correlacionar este hallazgo con la clínica se encontró en esta serie que 70% (7/10) de los infantes afectados vs 9% (4/44) de los infantes no afectados habían sido alimentados con miel. De 241 muestras de miel un 7.5% contenía el organismo.²³ Estudios más recientes²⁴, ²⁵ muestran que 7 de 12 de los infantes afectados recibieron miel. El organismo no pudo aislarse de 2 de las 7 muestras. De igual forma ningún otro artículo contenía el organismo. Otro alimento epidemiológicamente estudiado fue la leche. Se estudiaron los pacientes hospitalizados con botulismo infantil y los pacientes que mueren fulminantemente por la enfermedad y se correlacionó con la leche que recibieron: leche materna o leche de fórmula. Se encontró que los infantes que reciben leche materna son aparentemente protegidos contra la enfermedad fulminante, permitiendo la hospitalización del niño. Por otro lado, el mayor número de niños que murieron habían recibido leche de fórmula. Este estudio revela además que el ingerir hierro, ya sea en la leche o a través de otra fuente, parece predisponer a la enfermedad severa.^{22, 26} El rol del hierro es realmente especulativo, pues podría sólo reflejar que los niños que reciben leche de fórmula en Estados Unidos consumen mayormente fórmula con hierro. Se ha especulado que la leche materna protege a los infantes que sufren de botulismo infantil de la enfermedad mortal. Se ha pensado que la leche protege por sus factores inmunológicos (IgA, la presencia de leucocitos, lactoferrina y complementol) y por su efecto en la colonización de la microflora entérica.26, 27

Presentación Clínica

Pickett et al describen el síndrome de botulismo infantil por primera vez en el 1976.² Este síndrome se caracteriza por un historial de estreñimiento de varios días de duración, seguido de debilidad muscular

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descendente y progresiva, afectando mayormente los pares craneales 1X-XII, y ocasionado debilidad o parálisis de los músculos de la lengua y faringe. La afectación de estas áreas puede provocar obstrucción de las vías respiratorias y asfixia. Estos infantes presentan además dificultad para alimentarse, ptosis, dificultad para mantener la cabeza erecta, y el tono del esfinter anal está disminuido. 14, 12, 26 En la mayoría de las series, el estreñimiento era la presentación más común de la enfermedad.

En el botulismo infantil la parálisis fláccida producida por la toxina comienza en la musculatura enervada por los nervios craneales y desciende, pero los signos de ptosis, oftalmoplegia externa e interna y la flaccidez de los músculos faciales son leves y pueden pasar desapercibidos. Los bebés se alimentan pobremente debido a que no pueden chupar ni tragar adecuadamente y se tornan irritables. Cuando son evaluados por primera vez por un médico se hace con frecuencia un diagnóstico de infección del tracto respiratorio alto, otitis media, moniliasis oral y se envía el paciente a su casa con medicamentos. 14, 16

A medida que la parálisis desciende, el llanto se torna más débil y se altera su tono. En algunos casos la debilidad y la falta de coordinación de los músculos de deglución, en adición a una disminución en el reflejo de la náusea, propicia el ahogo o la aspiración.

Hay casos en que el infante pierde el control de la cabeza debido a debilidad muscular e hipotonía generalizada. En este momento no hay duda que el bebé debe ser hospitalizado para ofrecer medidas de sostén, mientras se continúan los estudios y se busca la etiología de la debilidad. Usualmente estos pacientes son admitidos al hospital con una impresión diagnóstica de septicemia, deshidratación, infección viral, hipotonía idiopática o polineuritis²8 y casi nunca se considera el diagnóstico de botulismo infantil. Si la debilidad muscular progresa durante la admisión, llega a su nadir en 2-3 semanas persistiendo sin progresar por 2-3 semanas adicionales, luego comienza lentamente el paciente a recobrar su fuerza y su movimiento.

El curso de la enfermedad es variada, pero por lo general la debilidad continúa y llega a un máximo en una a dos semanas. Luego el paciente mejora lentamente a menos que no hayan complicaciones tales como infecciones, hiponatremia, fallo respiratorio necesitando intubación, pneumotórax a tensión secundario a fistula broncopleural o enterocolitis necrotizante.⁴

Se ha observado que pacientes hospitalizados en California tienen una estadía en el hospital más prolongada cuando la enfermedad es causada por la toxina A que en aquellos causados por la toxina B. 16 Esto sugiere que la enfermedad causada por la toxina tipo A es potencialmente más severa.

Estudios Diagnósticos

Un gran porciento de los infantes presenta estudios de laboratorio normales incluyendo el contaje de células blancas, urinálisis, electrolitos en suero, la química y celularidad del líquido cefaloraquídeo y la toxicología.

El diagnóstico de botulismo infantil se debe considerar

en cualquier infante menor de seis meses previamente saludable que presenta un historial de estreñimiento seguido por debilidad, dificultad para chupar, tragar, llorar o respirar.

El diagnóstico positivo se hace al aislar *C. botulinum* de las heces, ya que este organismo no es parte de la flora intestinal normal. La toxina puede identificarse si la cantidad de heces es adecuada.

Thompson y Midura pudieron aislar el organismo y/o la toxina de las heces de todos los infantes con la entidad clínica.²⁵, ¹² Thompson aisló el organismo y/o la toxina de 20 de un total de 88 infantes normales o con una condición no compatible con el botulismo. La toxina y el organismo se vio simultáneamente en dos de los pacientes.¹²

Es importante señalar que aún después de recuperarse el paciente, éste puede continuar excretando el organismo y la toxina por varias semanas o meses. Eventualmente se logra eliminar el *C. botulinum* de la flora fecal.

El electromiograma también ayuda al diagnóstico de botulismo infantil, ya que demuestra un patrón característico: potenciales de acción abundantes, de corta duración y pequeña amplitud. El hecho de que este patrón esté ausente no excluye el diagnóstico de botulismo infantil.

Manejo

El tratamiento recomendado al presente para botulismo infantil consiste de una terapia de sostén meticulosa, haciendo énfasis en mantener la nutrición y la higiene pulmonar. 14, 29 El arresto respiratorio súbito ocurre en una tercera parte de los casos y por tal razón, estos pacientes deben tener acceso inmediato a una unidad de cuidado intensivo. Allí se vigilan para episodios de apnea y bradicardia. Los pacientes deben permanecer en esta unidad hasta que recobren su habilidad para respirar, toser y tragar espontanea y adecuadamente.

En los casos en que se requiere intubación por fallo respiratorio, Wolfe recomienda traqueostomía temprana para evitar las posibles complicaciones asociadas a una intubación prolongada.³⁰

La alimentación se lleva a cabo utilizando intubación gástrica y se continúa hasta que el infante pueda tragar adecuadamente.

Debido a que no se conoce si el *C. botulinum* presente en las heces pueda infectar otros infantes o adultos por transmisión fecal-oral, se recomienda establecer las precauciones usuales con el manejo de material fecal en la hospitalización. En el hogar se debe mantener un buen lavado de manos y adecuada eliminación de los pañales desechables, ya que se continúa excretando el organismo por semanas y hasta meses.

El uso de antitoxina en el botulismo infantil necesita más estudio. Hasta el momento no se utiliza rutinariamente, ya que no se ha encontrado toxina circulante en pacientes con botulismo infantil salvo un caso³¹ y sabemos que la antitoxina sólo actúa con la toxina libre en circulación. Además, la antitoxina del botulismo es derivada del suero de caballo y puede ocasionar efectos adversos de tipo de hipersensitividad.

En el presente, no hay indicación para el uso de

antibióticos. Se ha observado que la administración de penicilina o sus derivados por boca, o parenteral no ofrece beneficio clínico ni erradica el organismo o la toxina del intestino. También se ha observado en algunos casos que el uso de aminoglucósidos parenteral puede actuar sinergísticamente con la toxina en la unión neuromuscular y exacerbar la parálisis.³², ³³

Por último, los antibióticos administrados por boca pueden alterar la flora intestinal de tal forma que propicie el sobrecrecimiento de *C. botulinum* empeorando así la enfermedad.

Relación del botulismo infantil con muerte súbita infantil. Se ha sugerido que pueda existir una relación entre botulismo infantil y muerte súbita infantil, ya que ambas entidades comparten ciertas características en común. Se sabe que el mecanismo de acción y la potencia de la toxina puede llevar a una parálisis súbita de los músculos de respiración que puede resultar en una muerte súbita inesperada.²⁹, ³⁰

En estudios realizados durante el 1977, se estudiaron para la presencia de *C. botulinum* y su toxina, los especímenes de autopsias de 280 infantes que murieron de causas variadas. Se aisló el organismo de 10 infantes que murieron súbitamente y 2 de éstos tenían la toxina. La causa de muerte en 9 de estos 10 casos fue atribuída a muerte infantil súbita. En un grupo control de 68 pacientes que murieron de causas específicas, no se encontró el organismo ni la toxina. ¹⁷ Estudios subsecuentes en Utah y Washington han reportado *C. botulinum* en casos de muerte infantil súbita y no en casos controles.²⁹

Otra observación que ha sido reportada y que sugiere que el botulismo infantil tenga un papel importante como factor etiológico en el síndrome de muerte infantil súbita, es la distribución de las edades de ambas entidades. El pico de incidencia de muerte infantil súbita ocurre entre los 2 y 4 meses de edad, similar a los casos de botulismo infantil reportados en la literatura.¹⁷, ²⁷

Se ha postulado que la toxina de *C. botulinum* que ha sido producida en el intestino del infante puede causar la muerte súbita del bebé al debilitar o paralizar los músculos de la lengua y de la faringe, causar obstrucción parcial de las vías respiratorias y resultar en hipoxemia. La hipoxemia puede debilitar aún más estos músculos y producir obstrucción total de las vías respiratorias y causar la muerte súbita. Es obvio, sin embargo, que existen varias interrogantes y que es posible que el botulismo infantil sea una de las entidades que pueden producir el síndrome de muerte infantil súbita, pero que existan otros procesos infecciosos o fisiológicos que todavía no conocemos y que pueden sumarse a las causas del síndrome de muerte súbita.¹⁷

Quedan por resolver una serie de preguntas epidemiológicas, clínicas y patofisiológicas que ayudarán a definir entre otras cosas la verdadera incidencia del botulismo infantil, otros posibles vehículos de transmisión de las esporas, un tratamiento más efectivo utilizando antibióticos específicos en combinación con una inmunoglobulina botulínica derivada del hombre y sobre todo posibles medidas de prevención.

Botulismo Infantil en Puerto Rico

En estudios realizados en los Estados Unidos se ha

encontrado que hasta un 10% de la miel que se vende en supermercados está contaminada con esporas de C. botulinum.34 Es por esta razón que no se recomienda alimentos con miel a niños menores de 6 meses. Sin embargo, no se han realizados estudios epidemiológicos similares en Puerto Rico. Posiblemente no se han reportado casos en Puerto Rico por el bajo grado de sospecha clínica y la dificultad de hacer el diagnóstico definitivo. Sin embargo, de sospecharse un caso de botulismo infantil se debe consultar a un especialista de enfermedades infecciosas y ponerse en contacto con el Instituto de Laboratorios del Departamento de Salud (Tel. 767-6060), para el procesamiento adecuado de las muestras de suero y heces del infante. Este laboratorio se encarga de someter las muestras para cultivo y detección de la toxina al Centro de Control de Enfermedades en Atlanta.

Summary: The syndrome of infantile botulism is an infectious disease caused by the ingestion of *Clostridium botulinum* spores. Once in the intestines, the spores may germinate and produce the toxins responsible for the clinical picture. This syndrome is restricted to children older than 22 days and younger than 13 weeks. The clinical picture is characterized by constipation and general weakness, which in severe cases may progress to respiratory failure.

Treatment of these patients consist of supportive measures. Many clinicians recommend early tracheostomy and ventilatory support to prevent sudden death secondary to respiratory arrest.

Reconocimiento

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ASOCIACION PUERTORRIQUEÑA DEL PULMON

CAMPAMENTO DE VERANO PARA LA EDUCACION Y REHABILITACION DEL NIÑO ASMATICO (V.E.R.N.A.)

Objetivo:

Los Campamentos V.E.R.N.A. tienen como objetivo el educar y promover la rehabilitación de niños que padecen de asma bronquial en Puerto Rico. Para lograr dicho objetivo lleva a cabo actividades educativas, deportivas, recreativas y culturales que ayuden a mejorar la condición física y emocional del niño.

V.E.R.N.A. ¿Para quién?

Los campamentos van dirigidos hacia aquellos niños de ambos sexos con asma que por su severidad limitan significativamente su asistencia a la escuela y su participación en actividades de su edad. Incluye además aquellos niños que requieren visitas frecuentes a Sala de Emergencia o que por su condición se ve afectada la relación del niño con la familia misma. En V.E.R.N.A. se ofrecen los servicios de enfermería todo el tiempo.

Un grupo de médicos especialistas evaluarán diariamente a los niños participantes que así lo requieran.

Cuenta además con un director de deportes dinámico y personal especializado para el desarrollo de las actividades.

Requisitos:

- 1- Niños que padezcan de 6 o más episodios asmáticos al año, que requieran medicamentos diarios o vacunación semanal para estar libre de síntomas.
- 2- Niños de ambos sexos entre las edades de 8-12 años (no haber cumplido los 13).
- 3- Complementar la forma de solicitud en o antes de la fecha límite.
- 4- La participación de por lo menos uno de los padres o encargados en una actividad educativa y de orientación.

Dale la oportunidad a tu niño de vivir unas experiencias inolvidables que no sólo le servirán para recrearse sino para mejorar su salud física y mental. Para mayor información, comunícate con la Asociación Puertorriqueña del Pulmón más cercana:



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Aztreonam in the Treatment of Soft Tissue Infections Including Diabetic Foot Infections

Amaryllis Torres, M.D. C.H. Ramírez-Ronda, M.D.

The effectiveness and safety of aztreonam were evaluated in 23 patients with acute soft tissue infections including cellulitis, ulcers, abscesses and wound infections. Sixteen patients received 1 gm of aztreonam intravenously every 8 hours, 5 patients received 2 gm of intravenously every 8 hours, and 2 patients received 0.5 gm intravenously every 8 hours. Twenty patients received concomitantly nafcillin and 3 clindamycin at a dose of 2 gm intravenously every 4 hours and 0.6 gm intravenously every 6 hours, respectively. Most patients were seriously ill with underlying conditions like diabetes mellitus in 19/23 (82%), with a mean duration of the diabetes of 14 years (range 2 to 40 years). Escherichia coli was the most frequent organism isolated. The clinical response was a cure in 23/23 treated patients. Bacteriological response was a cure in 20/23 patients. There were three bacteriological failures: the first one was a superinfection with Pseudomanas maltophilia, the second was a hospitalacquired pneumonia, and the third was a superinfection with mixed organisms (Enterococci, Staphylococcus aureus and Enterobacter aerogenes). No serious adverse effects were documented. Aztreonam was found to be an effective, safe and valuable agent in the treatment of acute soft tissue infections caused by susceptible aerobic gramnegative bacilli.

Aztreonam is a totally synthetic monocyclic beta-lactam antimicrobial agent that belongs to the monobactam family, which has demonstrated an excellent activity against common gram-negative bacterial pathogens including Enterobacter species, Klebsiella species, and indole-positive strains of Proteus species. The rarity of resistance to Aztreonam among enterobacteria, together with its activity against highly carbenicillinresistant strains of Pseudomonas aeruginosa, which produces Beta-lactamase constitutively, and against Beta-lactamase-producing strains of Haemophilus influenzae and Neisseria gonorrhoeae suggests that the compound possesses a high degree of resistance to beta-lactamases. Aztreonam totally lacks activity against gram-positive strains and against anaerobic bacteria.

The present study was performed inorder to evaluate the safety and efficacy of Aztreonam in the treatment of acute soft tissue infections caused by susceptible gramnegative microorganisms.

Materials and Methods

Patient Selection and Studies. All patients admitted to the San Juan Veterans Administration Medical Center (Puerto Rico) with clinical evidence of acute severe bacterial infections of the skin and soft tissue, caused by microorganisms know or presumed susceptible to Aztreonam, were requested to participate in the study. The study was conducted between February and August 1983. Patients were excluded from the study in they had any of the following conditions: 1) history of Type I or anaphylactic reaction to penicillins, 2) known hepatic dysfunction, defined as SGOT or SGPT more than two times the upper limit of normal, or total serum bilirubin more than 3 mg/dl, 3) lactating or pregnant women, 4) granulocytopenia (absolute neutrophil count < 1000 per mm³), 5) patients who required hemodialysis or peritoneal dialysis, 6) concurrent severe disease, such as neoplastic disease, that may limit survival during the period of study, 7) patients legally or mentally incapacitated, 8) patients on effective antibiotic therapy 72 hours prior to enrollment. After a written informed consent was obatained, the patients were enrolled and appropriate culture of the blood and the infection site were performed. The cultures were repeated 48 hours after initiation of therapy and after completion of therapy, if the investigator considered it necessary. The following laboratory tests were performed before, during, and after completion of therapy: complete blood count and differential, urinalysis, platelet count, blood urea nitrogen, serum creatinine, serum calcium and phosphorus, serum glucose, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum alkaline phosphatase, serum creatinine phosphokinase, total bilirubin, prothrombin time and partial thromboplastin time.

Bacteriological Studies. Cultures were processed by the clinical laboratory using standard techniques.⁴ Bacterial isolates were identified by standard microbiological methods.⁵ Susceptibility testing was performed by using the Kirby-Bauer method⁶ with a 30 ug Aztreonam disk. Organisms were considered susceptible to Aztreonam if the inhibition zone was equal to or more than 20mm and resistant if it was 14mm or less. In addition, all pathogens isolated were tested by serial two-fold dilution for minimal inhibitory concentrations (MIC) of Aztreonam

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using the broth microdilution method.7

Administration of Antibiotic. Aztreonam (supplied by The Squibb Institute for Medical Research, Princeton, New Jersey) was administered parenterally to all patients. Five patients received 2 gm intravenously every 6 hours, 16 patients received 1 gm intravenously every 8 hours, and 2 patients received 0.5 gm intravenously every 8 hours. Median duration of treatment was 12 days (range 6 to 32 days). Twenty patients received concomitantly nafcillin and 3 clindamycin at a dose of 2 gm intravenously every 4 hours and 0.6 gm intravenously every 6 hours, respectively.

Clinical and Bacteriological Response. The patient's clinical response was considered: 1) a cure, if there was a defervescence and complete resolution of signs and symptoms of infection, 2) partial response, if there was a substantial or temporary improvement in signs and symptoms without complete resolution, and 3) failure, if there was a persistence or progression in signs or symptoms of infection. Bacteriological response was considered: 1) cure, if there was eradication of the original causative organism, 2) failure, if there was failure to eradicate the original causative organisms, and 3) superinfection, if there was a development of infection at the original site due to a pathogen which was not recognized as the original causative organism, and 4) subsequent infection, if there was a development of infection at any site other than the original primary one.

Results

Patient's Characteristics. Twenty-three patients were enrolled in the study. All were males with a mean age of 59 years (range 45 to 80 years). All patients (100%) had underlying diseases, such as diabetes mellitus in 19 with a mean duration of 14 years (range 2 to 40 years), cardiovascular disease in 4, chronic renal insufficiency in 4 and 1 each with renal transplant, neurological illness or rheumatoid arthritis.

Site of Infection and Etiology. All 23 patients had acute soft tissue infections. All had cellulitis in the following locations: lower extremities 20/23, and one each of scalp, abdominal wall and perianal region (Table I). The infections were classified as severe requiring hospitalization. Cellulitis with other associated conditions such as abscesses, ulcerations, or surgical wound infections was found in 19/23 patients.

TABLE I

Infection Site	Number of Patients
Foot	14
Stump	4
Leg	2
Scalp	1
Abdominal Wall	1
Perianal abscess	1
Number with osteomyelitis	9
Surgical procedures	
Incision and drainage	7
Amputation	9

The culture results and the minimal inhibitory concentrations (MIC) in ug/ml are shown in Table 2. The most common pathogen isolated was Escherichia coli, recovered from 7 patients. The next most frequent organisms recovered were: Klebsiella pneumoniae (6 cases), Serratia marcescens (3 cases), Proteus mirabilis (3 cases), and Pseudomonas aeruginosa (2 cases). The following microorganisms were recovered once in the studied cases: Morganella morganii, Citrobacter freundii, Citrobacter diversus, Pseudomonas maltophilia and Enterobacter aerogenes. Eighty-eight percent of the gram-negative organisms recovered in this study were inhibited by 1 ug/ml or less of Aztreonam, 100% of the Pseudomonas aeruginosa by 4 ug/ml or less of Aztreonam and the Pseudomonas maltophilia and the Enterobacter aerogenes were resistant to Aztreonam with an MIC greater than 128 ug/ml.

TABLE II

Organisms	No. of Strains	MIC's Mean (ug/ml)
Gram-negative		
Escherichia coli	7	0.125
Klebsiella pneumoniae	6	0.125
Proteus mirabilis	3	
		0.125
Serratia marcescens	3	0.156
Pseudomonas aeruginosa	2	4
Morganella morganii	1	0.125
Citrobacter freundii	1	0.125
Citrobacter diversus	1	0.125
Pseudomonas maltophilia	1	128
Enterobacter aerogenes	1	128
Gram-positive		
Staphylococcus aureus	6	128
Enterococci		
(Streptococcus faecalis)	3	128

Six strains of Staphylococcus aureus and 3 strains of Enterococci with an MIC greater than 128 ug/ml to Aztreonam were recovered in these patients. The recovery of only 9/23 gram-positive strains in infections that are usually caused by mixed flora is probably related to the fact that many of the patients studied received Aztreonam after there was no evidence of clinical response or evidence of failure during or after receiving treatment with single antibiotics effective only against gram-positive cocci and/or anaerobic organisms.

Response to Therapy. The clinical and bacteriological responses according to the type of infection are indicated in Table 3. The clinical and bacteriological responses were similar irrespective of the type of infection. Clinical cure was observed in 23/23 (100%). All these patients had a disappearance of the symptoms and signs of infection. Twenty of 23, or 87%, of the studied patients were documented bacteriological cures. There were three bacteriological failures; the reason for these failures was the development of superinfection in two patients with cellulitis and osteomyelitis that were superinfected with Pseudomonas maltophilia and the second with mixed flora (Enterococci, Staphylococcus aureus, and Enterobacter aerogenes. The superinfecting microorganisms were

Response to Treatment with Aztreonam for Acute Skin and Soft Tissue Infections, by Anatomic Site or Type of Infection

	<u> </u>	lumber of Patients		
	Clinical Cure	Clinical Failure	Bacteriological Cure	Bacteriological Failure
Cellulitis Celulitis plus	4	0	3	1
Abscess	11	0	9	2
Ulceration	4	0	4	0
Surgical Wound	4	0	4	0

resistant to Aztreonam and sensitive to other specific antibiotics. The third failure was a patient who after responding from his cellulitis developed a subsequent infection compatible with hospital-acquired pneumonia. Unfortunately, no organisms were recovered from sputum cultures but the patient responded clinically to other appropriate antibiotics.

Toxicity. The administration of Aztreonam was well tolerated. No side effects were documented and there was no significant alteration in the hematological parameters including hematocrit, platelet count, prothrombin, time, partial thromboplastin time and no neutropenia was seen. There was no evidence of skin rashes or eruptions and no patient developed diarrhea or loose stools. We did not document a single episode of phlebitis, but the IV sites were changed every 48 hours, and scalp veins were used most frequently.

Discussion

In vitro susceptibility testing of clinical isolates to Aztreonam in our study confirmed other reports of the antibacterial activity of this antibiotic against gramnegative bacilli and gram-positive organisms.¹⁻³, ⁸⁻¹² In patients with skin and soft tissue lesions infected with complex inocula and mixed bacteriological flora, like that found in the diabetic patient, the activity of Aztreonam against gram-negative bacilli used concomitantly with agents active against gram-positive and/or anaerobic organisms appears to justify its use.

The effectiveness is demonstrated with clinical cures in 23/23 patients and bacteriological cures in 20/23 patients. Of the total of 23 patients treated, 3 were considered bacteriological failures; these failures could have been seen with any agent. Two of these patients were diabetics (one insulin dependant and the other noninsulin dependant) with cellulitis and osteomyelitis of right big toe. Both underwent surgical intervention to remove the osteomyelitic focus. One of them developed a superinfection with *Pseudomonas maltophilia* resistant to Aztreonam and the other developed clinical findings compatible with hospital-acquired pneumonia but, unfortunately, no organisms were recovered from the sputum cultures. The third failure was also an insulindependant diabetic with celullitis, abscess and gangrene and osteomyelitis of left big toe, who underwent a Ray amputation of the involved site. Afterwards, the patient developed a wound infection from which mixed organisms (Enterococci, Staphylococcus aureus, and Enterobacter aerogenes) were recovered.

In the present study Aztreonam was well tolerted by

the patients and no instance of hematological, hepatic or renal disturbance was associated to its administration.

Aztreonam was used as an agent effective against aerobic gram-negative organisms always in combination with an agent effective against gram-positive cocci and/or anaerobes where an aminoglycoside would have been considered. Under these conditions, this agent has proven to be effective in the treatment of soft tissue infections clinically serious since all of the patients had an underlying medical condition and 50% were insulindependant diabetics under moderate control.

We wish to bring two areas to the attention of the reader. First, that we did not observe any toxicity with this compound. Second, that there were instances of superinfection with *Pseudomonas maltophilia* and *Enterobacter aerogenes*. This should be looked into by other investigators once the agent is commercially available. Its activity against gram-negative organisms and its lack of serious toxicity makes Aztreonam a valuable, effective and well-tolerated agent for the treatment of patients with soft tissue infections caused by gram-negative bacilli susceptible to this agent.

La eficacia y seguridad de aztreonam fue Resumen: evaluada en 23 pacientes con infecciones agudas de tejido blando que incluían celulitis, úlceras, abscesos e infecciones de herida. Los pacientes recibieron las siguientes dosis endovenosas de aztreonam: 16 pacientes recibieron 1 gm cada 8 horas, 5 pacientes recibieron 1 gms cada 8 horas y 2 pacientes recibieron 0.5 gm cada 8 horas. Una segunda droga fue administrada concomitantemente con aztreonam por vía endovenosa en la siguiente forma: 20 pacientes recibieron nafcilina 2 gms cada 4 horas y 3 pacientes recibieron clindamicina 0.6 gm cada 6 horas. La mayoría de los pacientes estaban seriamente enfermos con condiciones subyacentes como diabetes mellitus de un promedio de duración de 14 años (límites entre 2 y 40 años) en 19 de 23 pacientes (82%). Escherichia coli fue el organismo aislado más frecuentemente. La respuesta clínica demostró cura en 23/23 pacientes tratados. La respuesta bacteriológica demostró cura en 20/23 pacientes. Hubo 3 fallas bacteriológicas: la primera fue una superinfección con Pseudomonas maltophilia la segunda fue una pulmonía adquirida en el hospital y la tercera fue una superinfección con flora mixta (Enterococo, Staphylococcus aureus y Enterobacter aerogenes). No se documentaron efectos adversos serios. Aztreonam resultó ser un agente efectivo, seguro y valioso en el tratamiento de infecciones agudas de tejido blando causadas por bacilos aeróbicos gram-negativos susceptibles.

Acknowledgment

We thank the Medicine and Surgical Housestaff and the Research Service of the Veterans Administration Medical Center of San Juan, Puerto Rico for their cooperation, Ms. Minerva Nevárez for her technical assistance, and Ms. Carmen D. Camareno for secretarial assistance.

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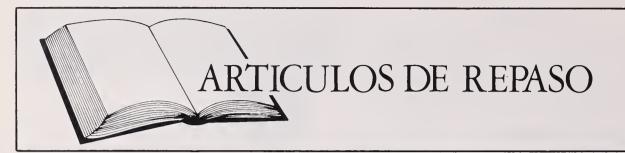
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Schistosoma Mansoni: Its Radiographic Manifestations*

Heriberto Pagán Saez, M.D.**

Abstract: The complex life cycle of Schistosoma mansoni gives rise to varied clinical and pathological manifestations. The radiographical changes are a reflection of the pathological processes caused by the reaction of the host tissue with the different stages of the parasite. The clinically detectable acute pulmonary phase is due to the passage of the larval stage through the lungs. The chronic phases present as portal hypertension syndrome, pulmonary hypertension syndrome, pulmonary cyanotic syndrome and systemic granulomata involving the pulmonary, gastrointestinal, retroperitoneal and central nervous systems.

Schistosomiasis was brought to America by African slaves during the slave trade and it is endemic to the Caribbean, north-eastern part of South America and Brazil. Manson's fluke is the only variety of medical significance in the western hemisphere.

HISTORICAL MILESTONES

Ebers papyrus - There is a description of a disease in Egypt presenting urinary symptoms, probably hematobiasis (S. hematobium).

- 1798-99 Egyptian campaign of the Napoleonic Army where many soldiers developed hematuria, probably S. hematobium.
 - 1851 Bilharz discovered worms in the mesenteric veins of an Egyptian farmer and named the parasite "Distoma haematobia".
 - 1858 Weinland proposed the name Schistosoma. ("Splitting of body")
 - 1859 Diesing proposed the name Bilharzia.
 - 1902 Manson discovered laterally spined eggs "in an African residing in the island of Antigua, West Indies.
 - 1904 González-Martínez established the first indication of endemicity of schistosomiasis in Puerto Rico.

- 1907 Sambon proposed the name S. mansoni for the parasite producing the "laterally spined egg".
- 1908 Piraja da Silva reported the presence of S. mansoni in Brazil.
- 1910 Ruffer discovered Schistosoma eggs in mummies 3000 years old.
- 1918 Leiper reported the results of the Bilharzia Mission in Egypt where differentiation of S. hematobium and S. mansoni as separate species was done.
- 1924 Faust and Meleney made the first comprehensive studies of S. japonicum in the Far East.
- 1925 Iturbe reported the presence of S. mansoni in Venezuela.
- 1934 Faust studied S. mansoni in Puerto Rico.
- 1936 Pons made the first clinical study of the disease in Puerto Rico. World War II Resulted in renewed interest in schistosomiasis in the Pacific (S. japonicum) and in the Caribbean (S. mansoni). The Selective Service considered schistosomiasis a disabling disease and deferred recruits on this basis.
- 1937 Koppisch described the foreign body type of reaction between the host and the parasite eggs resulting in a granuloma; the "pseudo tubercle".
- 1949 Vogel and Minning developed the CHR (Cerkarien-Hullen-Reaktion).
- 1951 Ottolina established the anatomical reason for the efficacy of the rectal biopsy. He found the greater concentration of sub mucosal eggs 9 cm. from the anus. (Houston valve)
- 1954 Oliver-González developed the Circum-oval Precipitin Test.
- 1962 García-Palmieri and Marcial-Rojas described the clinicopathological changes of S. mansoni and included the description of the "angiomatoid" in the lung.
- 1963 Marcial-Rojas and Fiol described S. mansoni of the Central Nervous System.
- 1965 Sutherland described S. mansoni eggs in placenta.

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TERMS RELATED TO THE LIFE CYCLE

Miracidium - Free swimming form hatched from the schistosomal egg outside the human host.

Planorbis glabratus - Fresh water snail which is parasitized by the miracidium. The only intermediary host known in Puerto Rico.

Primary and Secondary Sporocysts - Stages of the miracidial metamorphosis in the snail resulting in the production of cercariae.

Cercariae - Free swimming stage that will penetrate the skin of the human host.

Metacercaria or Schistosomule - Larval stage in the human blood stream.

Gynecophoral canal - Longitudinal ventral groove in the adult male worm to accommodate the filiform female worm for copulation.

LIFE CYCLE AND CLINICAL STAGES

The life cycle starts with a "laterally spined egg" (fig. 1) that is transformed into a *miracidium* (fig. 2) outside the human host which in turn parasitizes a fresh water snail from which the *Cercariae* (fig. 3) emerge.

The free swimming cercaria penetrates the human skin upon contact with the infected waters and once inside the human host, the *metacercaria* reaches the venous system. The passage of *larvae* thru the lungs may trigger an endovascular hypersensitivity reaction simulating an asthmatic episode and a generalized allergic state with fever, myalgia and high eosinophilic counts.

Figure 4 shows a lateral chest film with multiple nodular patches in an 11 years old male with the acute pulmonary schistosoma phase. We know that almost all of these clinical presentations go unnoticed and are treated as bronchopneumonia, asthma, "tropical eosinophilic lung", and other clinically similar entities.

The larvae eventually reach the intrahepatic portal system where they mature and return, against the portal flow, into the mesenteric venules, mostly the hemorrhoidal plexus where copulation occurs and the mature female deposite the eggs in the vein lumen.



Figure 1

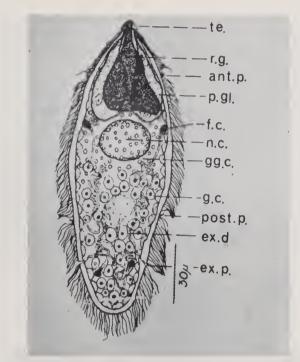


Figure 2



Figure 3



Figure 4

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Figure 5 shows a mature worm with the filiform female within the male gynecophoral canal and fig. 6 shows the worms inside the mesenteric venule. After *oviposition* the eggs will be distributed thru the venous system and interstitium.

The route of egg distribution and host reaction to the egg material will be demostrable as pathological processes which will be manifested clinicoradiologically. I have detailed six distribution routes that will be followed systematically in order to explain the different clinical and radiographical manifestations.

First Route: The eggs penetrate the vessel wall and traversing the interstitial tissues reach the intestinal lumen without a significant tissue reaction. In this case there are no changes except for a positive rectal biopsy. Fig. 7 shows eggs in submucosa of rectum after biopsy. Second Route: The eggs penetrate the vessel wall and generate a tissue reaction in the intestinal wall ranging from edema to granuloma formation.

Figure 8 shows thickened mucosal folds in a barium enema study due to interstitial edematous reaction.



Figure 5



Figure 6



Figure 7

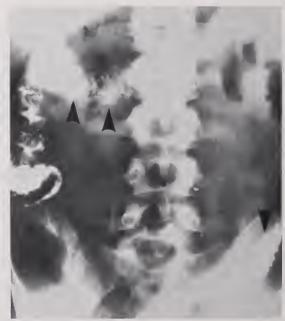


Figure 8

Figure 9 shows multiple granulomata that will be seen as "polypoid lesions" in the barium enema studies in fig. 10 and fig. 11.

A diffuse desmoplastic reaction leading to fibrosis may simulate "radiation proctitis as in fig. 12 or "chronic ulcerative colitis" as in fig. 13.

Uncommon gastrointestinal manifestations are gastric ulcer (fig. 14) and gastroduodenal fibrosis. Malabsorption syndrome due to small bowel disease and chronic pancreatitis have been described.

Third Route: The eggs are carried into the liver via the portal system where an endothelial reaction results in fibrosis (fig. 15) and granuloma formation (fig. 16). The fibro-granulomatous reaction obliterates the intrahepatic portal veins resulting in portal hypertension and the development of hepatofugal collaterals. Esophageal varices (fig. 17) and splenomegaly (fig. 18) are the most common radiographic features in portal hypertension. Fourth Route: The eggs follow the ascending lumbar venous system into the retroperitoneum, spinal cord and



Figure 9



Figure 10



Figure 11

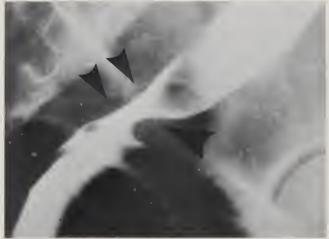


Figure 12



Figure 13



Figure 14

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Figure 15



Figure 16



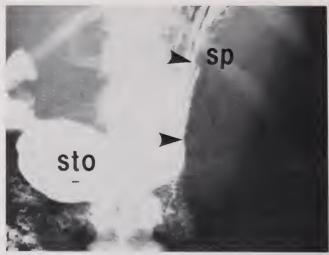


Figure 18

central nervous system previously described as the "ectopic lesions of Faust".

Figure 19 is that of a 7 years old girl which shows a retroperitoneal granuloma causing hydronephrosis. Figure 20 shows an egg in a spinal cord biopsy and fig. 21 a granuloma of the cord by myelography. We have had several young patients presenting with a clinical picture of "myelitis" in which circumoval tests of the spinal fluid have been positive.

Fifth Route: Eggs reach the lungs via natural collaterals, the azygos system or surgical porto-systemic shunts.

Involvement of the lungs with diffuse pulmonary granulomata will give rise to three distinct clinical pictures. All of the patients in this category have long standing portal hypertension and porto systemic shunts. For some unknown reason diffuse pulmonary granulomata may present with no significant pulmonary dysfunction, others with pulmonary hypertension and others, uncommonly, with a cyanotic syndrome.

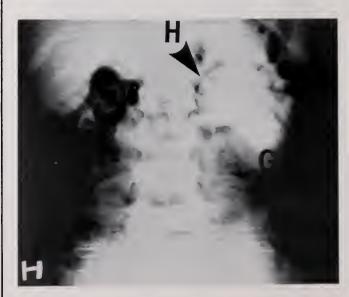


Figure 19

PULMONARY GRANULOMATA

This is a 30 years old male with portal hypertension, cough, dyspnea and eosinophilia. Observe the diffuse pulmonary nodularities in fig. 22 representing the pulmonary granuloma seen microscopically in figure 23.

GRANULOMATA WITH PULMONARY HYPERTENSION

This is a 42 years old male with portal hypertension and a pulmonary artery systolic pressure of 92 mm Hg with 95% oxygen saturation. Figure 24 shows cardiomegaly with a markedly dilated pulmonary artery. The autopsy specimen showed marked right ventricular dilatation.

GRANULOMATA WITH CYANOTIC SYNDROME

The cyanotic syndrome results from the formation of arteriovenous shunting at the site of the granuloma which is the "angiomatoid" described by Marcial-Rojas and García-Palmieri.

This is a 30 years old patient with cyanosis and arthralgia that presented clinical signs of pulmonary osteoarthropathy with a pulmonary artery pressure of 27 mmHg and 73% oxygen saturation. Figure 25 shows minimal cardiomegaly with no dilatation of the pulmonary artery.

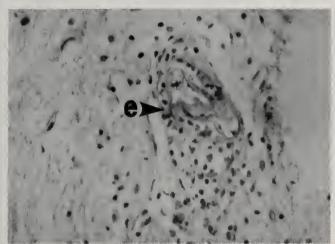


Figure 20

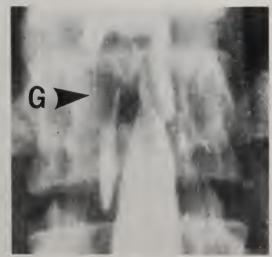


Figure 21



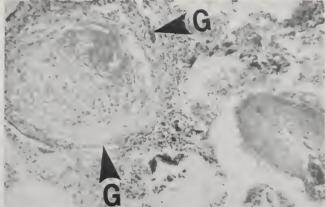


Figure 23

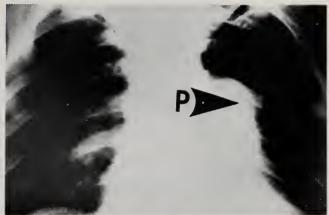


Figure 24



Figure 25

Conclusion

Schistosoma mansoni is the only species prevalent in the Americas. Large non-endemic foci occur in Miami, New York, New Jersey, Chicago, Boston and Philadelphia. Think of schistosomiasis in Puertoricans presenting with one or several of the clinical signs: esophageal varices, splenomegaly, portal hypertension, ascites (liver failure), pulmonary nodules, "myelitis" syndrome, cor pulmonale, hypertrophic osteoarthropathy.

Resumen: El complicado ciclo de vida de *S. mansoni* produce variadas manifestaciones clínicas y patológicas. Los hallazgos radiográficos reflejan los cambios patológicos causados por la reacción alérgica entre el huésped y las diferentes etapas del parásito.

La fase aguda pulmonar se debe al paso de la larva a través de la trama vascular pulmonar.

Las fases crónicas se manifiestan como los síndromes de hipertensión portal, hipertensión pulmonar, cianosis pulmonar y granulomas en el sistema pulmonar, gastrointestinal y retroperitoneal así como en el nervioso central y periférico.

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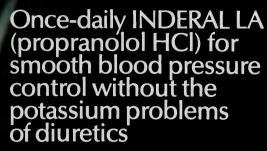
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INDERAL* LA brand of progranolof hydrochloride (Long Acting Capsules)
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride inderal LA is available as 80 mg. 120 mg. and 160 mg capsules
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.
INDERAL LA Capsules (80. 120, and 160 mg) release propranolol HCI at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are tairly constant for about twelve (12) hours then decline exponentially.

prophatoloi, destaining floith residuent rate of absorption to prophatoloid. Over a twelny-tout period, blood levels are fairly constant for about twelve (12) hours then decline exponentially INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect. INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output. (2) inhibition of reini release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase inhibiting. It readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolof generally reduces the oxygen requirement of the heart at a convention of the peripheral proprandial of offerts by blocking the activities and a supplier of the heart at a convention of the peripheral proprandial of the forth by blocking the activities and a supplier of the peripheral proprandial

treatment of hyperfensive patients
In angina pectoris, proprianofol generally reduces the oxygen requirement of the heart at
any given level of effort by blocking the catecholamine-induced increases in the heart rate,
systolic blood pressure, and the velocity and extent of myocardial contraction. Proprianolo
may increase oxygen requirements by increasing left ventricular fiber fength, end diastolic
pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade
is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

Increased work capacity
In dosages greater than required for beta blockade. INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain. The mechanism of the antimigratine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the paid vessels of the brain. Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm. Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of

entensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated he long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache efficacy of propranolol in the treatment of a migraine attack that has started has not been ablished and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of patients by the paties tenosis expensible for target of experience of other stees and used.

hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of

effectiveness of propration hydrochloride in this disease appears to be due to a reduction the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree bfock, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

INDERAL WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart supplies.

muscies IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIES, there have been reports of exacerbation of angina and, in some cases, myocardial infaction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) —
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA
BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors
MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy
prior to major surgery is controversial it should be noted, however, that the impaired ability of
the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesea and surgest procedures. sia and surgical procedures







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INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

hypotension Diriccity in starting and maintaining the nearboear has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranofol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranofol does not distort thyroid function tests IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranofol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranofol.

PRECAUTIONS. General Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCI) is not indicated for the treatment of

hepatic or renal function INDERAL (propranolol HCI) is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia vertigo syncopal attacks or orthostatic. which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic

which may result in hypotension, marked order, yet the hypotension Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was

levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug *Pregnancy** Pregnancy** Category** C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *Nursing Mothers** INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman *Pediatric Use** Safety and effectiveness in children have not been established *AVERSE REACTIONS**. Most adverse effects have been mild and transient and have rarely required the withdrawal of theraby.

rarely required the withdrawal of therapy

Cardiovascular bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura arterial insufficiency, usually of the

tension, paresthesia of hands, thrombocytopenic purpura arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, halfucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been

Miscellaneous alopecia LE-like reactions, psoriasiform rashes, dry eyes, male impo-tence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol)

Involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol posage AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Fetitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval. HYPERTENSION.—Dosage must be individualized. The usual initial dosage is 80 mg. INDERAL A once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS.—Dosage must be individualized. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

If freatment is to be discontinued, reduce dosage gradually over a period of the MigraNINGS)

MIGRAINE—Dosage must be individualized. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose. INDERAL LA therapy that the druin gradually over a period of should be discontinued. It may be advisable to withdraw the drug gradually over a period of

Several Weeks HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use rmit adequate directions for use

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Presentación de Casos

Gilles de la Tourette Syndrome: An Underdiagnosed Disorder

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Abstract: Gilles de la Tourette Syndrome is a disorder characterized by chronic multiple motor and vocal tics.

We present five cases followed by a discussion of the disease with emphasis on its recognition and differential diagnosis.

Tourette's Syndrome (T.S.) is an involuntary movement disorder characterized by onset in childhood of multiple motor tics and vocalizations.

It is generally considered to be a rare condition. As physicians have gained familiarity with its manifestations and as exposure in the lay press has become widespread, the observed incidence is increasing rapidly and the rarity of the disorder can be questioned.

We present five cases of T.S. evaluated at the Pediatric and Adolescent Neurology Clinics of the San Juan City Hospital between 1980-1984, followed by a discussion on the subject.

It is our interest to alert the medical community to detect the undiagnosed cases that are not benefiting from treatment.

Case No. 1

Was a previously healthy 16 year old female who at age 10 developed exaggerated eye blinking. Six months later it dissapeared and was replaced by motor tics involving the extremities, neck, mouth; plus vocal tics that waxed and waned in severity (Tables 1 and 2). One year after onset she was evaluated at the New York Presbyterian Hospital where she was diagnosed as TS. After treatment with haloperidol (Haldol) was initiated, her tics were significantly controlled.

She was first seen at our clinics in November 1980, at age 12. Her only positive findings on neurological examination were a tendency to keep her mouth open and mild slowness of speech. Psychological testing showed an average intelligence. Evidence of mild dyslexia and dysgrafia was found. Psychiatric evaluation revealed no abnormalities.

Case No. 2

Was a 15 year old male who was doing well until age 9 when he started making a sound like if he had hiccoughs ("uh, uh"). His parents thought that he had asthma and the patient was evaluated by several physicians. No evidence of respiratory disease was found. The vocal sounds slowly resolved and new tics involving the nose, eyes, and face, in that order, appeared (Tables 1 and 2). The facial tics later stopped, but at age 12 he started again with vocalizations. He was hospitalized one week, but no abnormality was found. The focal tics decreased in severity until age 14 when they again became prominent. At that time the vocal tics were accompanied by head movements, facial tics, shoulder shrugging, and movements of hips and abdomen (Table 2).

Interestingly, this patient also had simple partial motor seizures since age 13, well controlled on phenytoin (Dilantin). His electroencephalogram (EEG) was normal. The tics were not affected by phenytoin, but responded well to haloperidol.

Neurological, psychological and psychiatric examinations are normal.

Case No. 3

Our third case was a 10 year old male was in good health when, at age 7, his parents noticed tic-like jerks of head, face, trunk, arms and legs. The tics varied in severity and location. He was evaluated at our neurology clinic on April 1984, at age 10. At that time the patient had developed throat-clearing sounds, repetitive eye movements, back and forth movements of the scalp, lip pursing and tongue protrussion (Tables 1 and 2). On initial evaluation it was also noted that the would move his nose then touch it.

There was a history of his father having tic-like behavior (eye blinking). Besides tics, the neurological

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examination was normal, and so was the psychiatric and psychological evaluations.

At the time of evaluation the tics were not severe, and no medication was prescribed.

Case No. 4

Patient No. 4 is a previously healthy 10 year old boy who developed eye blinking and repetitive convergence of eyes at age 3. Two years later he developed coprolalia and moaning sounds. Tics varied in intensity and at age 6 the following new symptoms appeared: making noises like a car, barks, throat clearing, sniffing, echolalia, palilalia, facial tics, squeals and motor tics of trunk, arms and legs. The tics were most evident, when the patient was concentrated playing or watching television. He sometimes started saying "blah, blah, blah" while watching televison, and repeats many times the word "what". Parents had also noticed that their son tried to touch all he sees, as if he could not control it.

He was evaluated at our clinic at age 9, six years after onset of symptoms (Table 1). Neurological examination, psychiatric and psychological evaluations were all normal.

Case No. 5

Our last case was a previously healthy 12 year old boy who at age 4 started with facial tics, to be followed by making sounds like a car, airplane, horse, throat clearing; and echolalia. In the ensuing years other symptoms with changing severity appeared, such as: head movement, mouth and tougue movement, clapping and jumping. Sometimes a tic was replaced by another, only to reappear months or years later. Lately, this boy has been seen to hit his head lightly with his hand and to do rocking movements while seated.

This patient, like patient No. 2, has a seizure disorder concurrently with TS. His seizures were of the partial complex type under good control with carbamazepine (Tegretol). The above mentioned involuntary movements and vocalizations were not associated with changes in the state of consciousness. Carbamazepine did not have any effect on the tics.

Neurological examination was normal. EEG revealed an epileptic focus in the right pre-frontal region. Psychological evaluation disclosed an attention deficit disorder with disorders in reading and writing. As with all the other patients, no psychopathology was found on psychiatric consultation.

TABLE I

Case Summaries						
Case No.	1	2	3	4	5	
Sex.	Female	Male	Male	Male	Male	
Age (in years)	16	15	10	10	12	
Age at onset of symptoms	10	9	7	3	4	
Time from onset to diagnosis (in years)	1	6	3	6	7	
Initial Symptoms (2)	eye-blinking	vocal sound ("uh, uh")	tics involving head, face, trunk, arms and legs	eye blinking, eye covergence	facial tics, sounds	
Coprolalia	No	No	No	Yes	No	
Echolalia	No	No	No	Yes	Yes	
Family hx of tics	No	No	Yes	No	No	
Neurological examination (excluding tics)	normal except for opened mouth and slow speech	normal	normal	normal	normal	
Psychological	Average intelligence, Mild dyslexia and	Above average	Average	Average	Above average intelligence, attention deficit disorder, deficit in writing and	
Evaluation	agraphia	intelligence	intelligence	intelligence	reading	
Evidence of psychia-						
tric Disorders	none	none	none	none	none	
Seizures	No	Partial simple motor	No	No	Partial Complex	
					Epilectic focus in right pre-	
EEG		normal			frontal region	

Cummulative Signs and Symptoms of Our Cases					
Case No. 1	No. 2	No. 3	No. 4	No. 5	
- eye blinking	- vocal sounds ("uh, uh")	- head tic	- eye blinking	- facial and head tics	
- tics of upper and lower extremities	- nose tics	- facial tic	- eye convergence		
- neck flexion	- eye blinking	- arm and leg tic	- shrieks	- car sounds	
- mouth opening and closing	- facial tics	- throat clearing	- car noises	- airplaine sounds	
- vocal sounds ("ah, ah, ah")	- head nodding	- eye movement	- barks	- horse sounds	
	- shoulder shrugging	- scalp movement	- throat clearing	- throat clearing	
	- movements of hips and abdomen	- lip pursing	- sniffing	- echolalia	
		- tongue protrussion	- echolalia tongue tics	- mouth and	
		- nose touching	- palilalia	- clapping	
			- coprolalia	- jumping	
			 motor tics involving the face, trunk, arms and legs 	- hitting the head - rocking	
			- "blah, blah, blah"		
			- repeats "que"		
			- touches objects		

Discussion

As illustrated by the above cases, TS can present a be wildering variety of signs ans symptoms that could be confused with psychiatric or organic disorders. It is important to be familiar with its diverse manifestations in order to reach an accurate diagnosis.

Etiology

The etiology of TS remains unknown. Recent reports have suggested that TS is related to and alteration of central nervous system neurotransmitter function. Among the proposed defects are abnormalities in the function of the striatal neurotransmitters dopamine, serotonin, acetylcholine and the neuromodulatory agent norepine-phrine.¹, ⁹, ¹¹ Dopamine has the most experimental support. It is postulated that dopaminergic hyperactivity is important in the genesis of symptoms. This theory is supported by the fact that the dopaminergic receptor blocker, haloperidol is effective in this disorder.¹, ³, ⁹, ¹¹

The beneficial action of clonidine, and adrenergic agonist that reduces central neuroadrenergic activity, has suggested the possible involvement of the noradrenergic systems.^{1, 9, 11}

Pathology

Only four pathological examinations of TS patients have been reported. No consistent pathological abnormalities were found.³, ⁹

A recent article proposes that the periaqueductal gray matter and midbrain tegmentum may be involved in TS.³ This is based on the fact that patients who have suffered from encephalitis lethargica showed vacalizations similar to those of TS. These include coprolalia, grunts, barks and squawks.³, ⁹ In encephalitis lethargica, the periaqueductal gray and midbrain tegmentum are the principal sites of involvement.

Electrophysiologic Studies

EEG abnormalities are reported in 60% of patients with TS but these are usually non-specific and no not aid in the diagnosis.^{1, 7, 9} One of our patients had and abnormal EEG (Patient No. 5), but it corresponded to coincident epilepsy.

We have two patients with both TS and seizures (Patients 2 and 5). Dr. Arthur Shapiro, Director of the Tourette and Tic Lab and Clinic at Mount Sinai Medical School in New York was asked of his experience with the association of TS and seizures. He states hat they have several TS patients with absence and major seizures, but the incidence appears to be what one would expect in a normal population. The incidence of epilepsy in our TS patients is unexpectedly high (20%). It is difficult to make conclusions about this fact due to the size of our sample.

The evoked responses in TS have recently been studied. Seventeen patients with varying severity of tics had visual, brainstem-auditory, and somatosensory evoked responses studies. No significant abnormalities were found.⁷

Neuroradiological Studies

No specific findings in computed tomography (CT Scan) or angiography have been reported.¹, ²

A recent study reported abnormalities in Positron Emission Tomography (PET Scan) studies of TS patients.² They found relative hypermetabolism in certain portions of the frontal and temporal lobes bilaterally. The glucose utilization in the basal ganglia averaged 16% above control levels. To our knowledge this is the first study of PET scanning in TS.

Clinical Features

The onset of TS is between the ages of 2 and 15 years, with a 3:1 male predominance. The initial symptoms, like the syndrome itself, is quite variable. The symptoms of TS begin with multiple tics in 49% of patients and with a single tic in 51%. In our patients 40% started with multiple tics and a single tic was the first symptom in 60%.

The most frequent initial symptom is an eye tic (42%) followed by a head tic (20%) or facial grimace (12%). A significant number begin with sounds or words (19%); 20% in our patients (Tables 3 and 4). Fairly complex movements can also be a manifestation of TS (Table 5).

TABLE III

Symple Motor Symptoms in TS

eye tic eye rolling forced starring involuntary gaze diviation facial tic lip biting mouth tic nose tic open - close mouth facial grimace tongue protrussion spitting licking head and neck tics shoulder shrugging arm and leg jerk trunk jerk abdominal jerk

TABLE IV

Sounds and Words in TS

throat clearing expiratory sound coprolalia echolalia palilalia whistle grunt bark snort shriek scream laugh noisy breathing sniffing squeal stutter words vocal sounds

TABLE V

Complicated Movements in TS

touching (self, others, objects) hitting jumping echopraxia skipping squatting kicking smelling (hands, objects, etc.) bang table throw object scratching kneeling trunk flexion deep knee bends extend arm bang head on floor dancelike movements

The symptoms characteristically change in severity and pattern over time. Since the disorder is of lifelong duration, a patient can have different manifestation at different times of his life. There are periods when there are very few symptoms and others when patients are socially incapacitating. Patients have control over their tics, to a certain degree. Usually, while in public they concentrate to inhibit their tics, especially those that are socially disturbing (e.g., coprolalia). When the patient is in a familiar environment or distracted in some non-ansiogenic task the symptoms return. These tics, like other involuntary movements, may be increased by stress. It is unusual that the patients manifest tics while in the physician's office, even if asked to simulate them. In these cases the diagnosis depends on a careful history.

A family history of some type of tic is found in 30% of cases, and families with several TS members have been reported. One of our patients (20%) has a relative with tics (his father), but no one with TS (case No. 3). The pattern of inheritance is not clear. 1, 6, 8, 9 Golden suggestes that simple tics and TS may represent "different positions on the same continuum and not distinct conditions".6

Coprolalia is the most famous and also the most interesting manifestation of TS. It is present in only 60% of cases. Coprolalia is pathognomonic but not essential for the diagnosis. Only one of our cases had this symptom. The average age of onset is 13.5 years and the average number of years between onset of TS and coprolalia is 6.4. It can rarely occur as the first sympton. Many patients have spontaneous remission of coprolalia without medication at an average age of 18.7 years. This is the most distressing symptom and, luckily, it is usually the first to disapear with haloperidol.

Echolalia and palilalia are also characteristic but are not required for the diagnosis.

All the symptoms of TS, including coprolalia, are completely involuntary. No psychopathology has been found. Patients have normal intellects. There are however, many patients with history of hyperactivity and specific learning dissabilities.³, ⁹ Two of our patients (No. 1 and 5) had these problems (Table 1).

Patients with TS have a high frequency of minor non-localizing neurological abnormalities^{1, 3, 4, 5, 9} (Table 6). Major neurological signs should suggest another diagnosis (Table 7). There is a higher than expected indidence of left-handedness or ambidexterity (Patient No. 3 is left-handed and Patient No. 4 is ambidextrous).

TABLE VI

Minor Neurological Sings in TS

unilateral dysdiadochokinesia pronator drift increase in tone or reflexes facial asymmetry chorea or choreathetoid movements snout reflex involuntary gaze deviation

TABLE VII

Differential Diagnosis of TS

simple tic disorder subacute multiple tic of chilhood or adolescence myoclonus partial complex seizures Wilson's Disease Sydenham's Chorea dystonic syndromes Hallervorden-Spatz disease

Diagnosis and Differential Diagnosis

The criteria for diagnosis of chronic multiple tic disorder or TS include:

- 1. age of onset between 2 and 15 years;
- 2. multiple, rapid, stereotypic and involuntary muscular and verbal tics;
- 3. fluctuating clinical course, symptoms wax and wane and slowly change;
- 4. voluntary effort can always reduce or completely control symptoms for brief periods and occasionally for prolonged periods but results in subsequent tension and ultimate increase in discharged symptomatology;
- 5. symptoms disappear during sleep and orgasm;
- 6. the illness is lifelong and chronic. At least one year since onset of symptoms must have passed to make the diagnosis.

Confirmatory but not essential for the diagnosis are:

- 1. Coprolalia
- 2. Copropraxia
- 3. Echolalia
- 4. Echopraxia
- 5. Palilalia

Frequent concomitants of the disorder but not essential for the diagnosis are:

- 1. history of hyperactivity or perceptual problems in childhood or organic stigmata in adulthood;
- 2. abnormal nonspecific EEG;
- 3. soft signs of neurological abnormality;
- 4. subtle signs of organic dysfunction on psychological testing.9

Due to the multiple manifestations of TS it has been confused with other conditions. We feel that a thorough history and neurological examination usually is enough to separate TS from other disorders.

Acute simple or transient tic of childhood is the most comon (12% incidence). Usually only one or two muscular groups are involved and the most frequent symptom is eye blinking. Involvement of more than one or two muscular groups or involuntary noises almost never occur. Symptoms spontaneously remit within 2 weeks to a year.

Chronic simple tics are similar to the above, except that the tic persists throughout life.

The features of subacute, persistent simple or multiple tics of childhood or adolescence are one two muscular or verbal tics which persist for longer than a year but disappear by or during adolescence. More extensive symptomatology, involving multiple, changing and fluctuating involuntary muscular movements, noises or words may occur. The disorder is indistinguishable from TS, except that the symptoms spontaneously remit by or during adolescence. The disorder is classified as TS only if the symptoms persist beyond adolescence and are lifelong. Other conditions that may be confused with TS are listed on Table 7.

Conclusion

The tic disorders represent a spectrum of disability ranging from simple transient tics to severe TS. Diagnosis depends on an awareness of their existence and differentiation from other disorders. A careful history and examination usually is enough to diagnose this not so rare disease.

Resumen: El síndrome de Gilles de la Tourette es un desorden caracterizado por múltiples tics motores y vocales. Presentamos cinco casos seguidos de una discusión de la condición con atención al dignóstico y diferencial.

Acknowledgment

The authors thank Mrs. Ramonita Cancel for her secretarial assistance.

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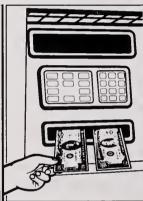
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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C. Angel F. Espinosa-López, M.D.

Una niña de 5 años de edad es hospitalizada para cateterismo cardíaco. Tiene un soplo cardíaco desde la temprana infancia, y en su historial pasado no hay evidencia de insuficiencia cardíaca ni de cianosis. Siempre ha sido una niña activa aunque su madre nota que se cansa más fácilmente que los demás compañeros de juego. Su crecimento y desarrollo ha sido normal pero con un aumento de peso lento. No hay historial de infecciones respiratorias frecuentes.

Al examen físico se aprecia una niña pequeña para su edad signos vitales normales. El PMI es palpable en el 5° espacio intercostal izquierdo a nivel de la línea media clavicular. La actividad ventricular derecha es palpable en la región apico-esternal. No hay frémito. El soplo es sistólico-eyectivo, rudo, grado 3/6 y se aprecia mejor en el 2° y 3er espacio intercostal izquierdos. Tiene una leve irradiación a la espalda. Se aprecia también un arrastre mesodiastólico en la parte media e inferior del reborde costal izquierdo. El S_1 es normal, el S_2 está ampliamente desdoblado y no varía con la respiración. El componente pulmonar del S_2 (P_2) está discretamente aumentando. No hay visce romegalia y los pulsos periféricos son normales. La Hb es de 12 gm. El electrocardiograma no demuestra hipertrofia de cámaras, solo un patrón rSR1¹ en los precordiales derechos y un eje QRS de + 100°. La radiografía de tórax revela una razón cadio-torácica de 50%, una convexidad en el segmento pulmonar y una circulación pulmonar discretamente aumentada.

El angiograma que se ilustra a continuación demuestra el defecto cardíaco de la niña.



Angiograma atrial izquierdo en la proyección hepatoclavicular. LA = atrio izquierdo; RA = atrio derecho; IVC = vena cava inferior; RSPV = vena pulmonar superior derecha.

¿CUAL ES SU DIAGNOSTICO?

Hospital Pediátrico Universitario, Departamento de Pediatría, Sección de Cardiología Pediátrica, Recinto de Ciencias Médicas, Universidad de Puerto Rico.

Comunicación Interatrial (Secundum)

La comunicación interatrial (CIA) tipo secundum es una de las cardiopatías congénitas más frecuentes, representa en el 7-8% de todas ellas. Tiene una incidencia mayor en el sexo femenino (2:1) y usualmente no se asocia con otras malformaciones cardíacas.

Se cree que en ocasiones este defecto se transmite como resultado de un trastorno genético, pues el mismo se halla presente en varios miembros de una familia. Holt y Oram² reportaron la existencia de familias en las cuales varios miembros tenían anomalías oseas de las extremidades superiores asociadas a CIA del tipo secundum. También en el síndrome de Rubinstein-Taybi se ha informado la presencia de CIA tipo secundum en sobre 50% de ellos.³

La presencia de la CIA junto con la diferencia en presiones entre el atrio izquierdo y el derecho ocasionan un corto circuito atrial. La dirección de este cortocircuito viene determinada por esa diferencia en las presiones atriales. A su vez las presiones atriales vendrán determinadas por la distensibilidad de sus respectivos ventrículos. En los primeros meses de vida el grosor de las paredes ventriculares izquierda y derecha son similares pero según va pasando el período neonatal disminuye la resistencia pulmonar y el grosor ventricular derecho. Ello suele ocasionar un aumento en el corto circuito de izquierda a derecha a nivel atrial. A pesar del aumento en el flujo pulmonar (en ocasiones 2-3 veces lo normal) la presión pulmonar suele mantenerse dentro de los límites normales hasta temprano en la vida adulta y los cambios en las capas media e íntima de las arterias pulmonares suelen ser leves y sin consecuencia clínica en estos pacientes. La aparición de hipertensión pulmonar irreversible al igual que la disfunción miocárdica son muy raras en niños con CIA tipo secundum.^{4, 5}

La mayoría de los niños con este defecto tienen un curso asintomático ya que el corto circuito de izquierda a derecha no suele ser mayor de 2:1 y la presión pulmonar es casi siempre normal. Si hay síntomas suelen ser fatiga leve y disnea. La frecuencia de disnea y fatiga es mayor en aquellos con un cortocircuito de izquierda a derecha mayor (Qp/Qs > 3) y en estos casos es que puede sobrevenir el fallo cardíaco.

El aumento en flujo sanguíneo através de la válvula pulmonar es el responsable del soplo sistólico-eyectivo rudo en el precordio superior que está presente en los pacientes con CIA secundum. El arrastre mesodiastólico presente en algunos casos es ocasionado por el aumento en el flujo sanguíneo através de la válvula tricuspidea por el corto circuito de izquierda a derecha a nivel atrial. El desdoblamiento amplio (>0.04 sec.) del S₂ es quizás el hallazgo auscultatorio de mayor valor diagnóstico en la CIA. Este desdoblamiento suele ser también "fijo" ya que no varía con la respiración. Es el resultado de un retraso en el cierre de la válvula pulmonar debido al vaciado prolongado del ventrículo derecho, causado por el aumento en volumen de ese ventrículo que produce el corto circuito de izquierda a derecha interatrial.

La CIA tipo secundum is compatible con una vida larga y se han reportado casos que llegan hasta los 70-80 años con este defecto.⁶ Los pacientes con este defecto en

su inmensa mayoría permanecen activos, contolerancia al ejercicio excelente y llevando a cabo una vida normal. Hay aún incertidumbre con relación a la historia natural y el manejo correcto de los pacientes con CIA pequeñas. En estudios donde se llevaron a cabo cateterismos cardíacos seriados a pacientes con este diagnóstico no se pudo demostrar deterioro hemodinámico ni anatómico en un seguimiento promedio de 10 años.⁷

El tamaño y posición de la CIA se demuestra muy bien haciendo una angiografía atrial izquierda en la proyección hepatoclavicular según ilustramos en la página anterior. Puede verse el material de contraste entrando al atrio derecho através de la parte central del septo interatrial en un plano horizontal según señalan las flechas en la ilustración.

La reparación quirúrgica del defecto es el tratamiento de elección en aquellos casos en que el mismo sea hemodinámica y anatomicamente significativo. La edad en que se debe llevar a cabo la cirugía va a depender mayormente de la experiencia del cirujano, aunque para los 4 años ya se debe haber reparado. La mortalidad y morbilidad de este defecto no es significativa y se sabe que aumentan en la vida adulta, por lo que la cirugía se debe realizar a la edad recomendada la cual tiene resultado excelente. Las disritmias postoperatorias son frecuentes, la mayoría de las veces son disritmias de origen supraventricular y trastornos de la conducción atrioventricular. Estos por lo regular son transitorios y pueden manejarse médicamente. Estas disritmias son particularmente frecuentes en pacientes operados de defectos interatriales del seno venoso, muy posiblemente por la proximidad del nodo sinusal.8 También se debe recordar la CIA es la segunda cardiopatía (en orden de frecuencia) en que suele aparecer el síndrome de "post pericardiotomía" luego del cierre quirúrgico del defecto.9

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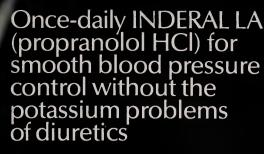
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Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.^{1,2} In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

beta-1/beta-2 blockade

Once-daily
INDERAL LA
(PROPRANOI OL HCL) NA ALINE







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80 mg

120 mg 160 mg

Please see brief summary of prescribing information on the next page for further details.

Once-daily For beta-1/beta-2 NDERAL LA (PROPRANOLOL HCI) LONG ACTING CAPSULES

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
INDERAL* LA brand of propranolol hydrochloride (Long Acting Capsules)
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol
hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules
CLINICAL PHARMACOLOGY, INDERAL is a nonselective beta-adrenergic receptor
blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When
access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and
vasodilator responses to beta-adrenergic stimulation are decreased proportionately.
INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCI at a controlled and
predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours
and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the
capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of
INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of
propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24)
hour period, blood levels are fairly constant for about twelve (12) hours then decline
exponentially.

propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period. blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect. INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL La has been therapeutically equivalent to the same mg dose of conventional effective beta blockade for a 24-hour period.

The mechanism of the anthippertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the anthippertensive action are (1) decreased cardiac output. (2) inhibition of renin release by the kindneys, and (3) diminution of fonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectons, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart at any given level of effort by blocking the catecholamine-induced increases in the heart at any given level of effort by blocking the catecholamine-ind

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the manage ment of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated to rithe long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of progranolol is in indicated for the prophylaxis of common migraine headache. The efficacy of progranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is confirandicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

INDEHAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics.

Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with dureftics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIES, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary aftery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA
BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors
MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy
prior to major surgery is controversial. It should be noted, however, that the impaired ability of
the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

sia and surgical procedures



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INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the ap-

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes in these patients, it may be more difficult to adjust the dosage of insulin THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

propranolol

PRECAUTIONS. General Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCI) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood ureal levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostation. which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility, Long-term studies in animals have

been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was

levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential is pregnant women INDERAL should be used during pregnancy only if the potential is the potential risk to the fetus Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman. Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy. Cardiovascular bradycardia. congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

tension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional liability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis, erythematous rash, lever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been

reported.

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serious membranes and conjunctivae reported for a beta blocker (practolol).

involving the skin, serous membranes and conjunctivae reported for a beta blocker (practofol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval. HYPERTENSION—Dosage must be individualized. The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—Dosage must be individualized. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose. INDERAL LA therapy

several weeks
HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too
limited to permit adequate directions for use

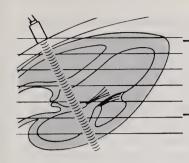
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ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., F.A.C.C.

This 51-year-old Mexican female had a history of typhoid fever. Her electrocardiogram suggested type C right ventricular hypertrophy.

Two-dimensional echocardiography revealed a large left atrium (LA) with the atrial septum bowed to the right, and a thickened, "stiffened" mitral valve. Doppler echocardiographic examination of the mitral valve was performed from the precordial apical position. Calculations were performed with an Apple II Plus computer (Cupertino, CA) and a prepared software disk program (Biodata. Davis, CA).



Figure 1

Figure 2

Figure 3

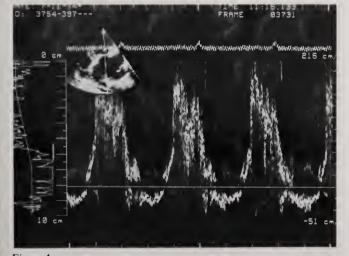


Figure 4

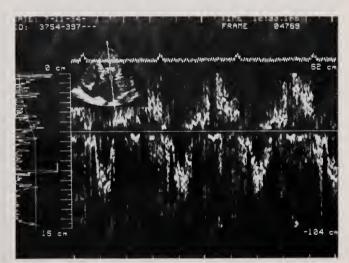


Figure 5

Questions

- 1. What are the diagnoses?
- 2. Quantitate the lesions.

University of Puerto Rico, Medical Sciences Campus Department of Medicine, Cardiology Section, Río Piedras, Puerto Rico 00936

Answers

Mitral Regurgitation (MR). Mild Mitral Stenosis (MS). Tricuspid regurgitation and secondary pulmonic regurgitation. Pulmonary hypertension (PH). Ventricular bigeminy.

Figure 1.Irex (Ramsey, NJ). Doppler echocardiogram, with continous wave (CW) "blind" angled probe at cardiac apex. Peak velocity (V) 2, 2.2 m/s (D wave), 1.49 m/s (A wave). There is a decreased diastolic slope and plateau of the tracing, and the contour of the premature beats differ from that of the sinus beats.

Pressure half-time: 134 mS. Mitral valve area 1.6 cm.²

Figure 2. Irex CW Doppler (CWD) with transducer at the apex. The negative velocities (flow away from the transducer) reflect MR, and differ in magnitude. Peak V=4.6~m/s (in jet); the regurgitant jet velocity tracing does not present an ideal envelope. There are a lower V and and slower increase in V in the premature beats. Pulmonary artery (PA) tracing (not illustrated) - PA large, peak V=80~cm/s. Time-to-Peak Velocity = 50, 70 ms. PA pressure by Swan-Ganz catheter = $\frac{60.75}{31-33}$ mean 41 mm Hg.

Aortic Flow (not illustrated) - peak V = 1 m/s, mean 18.4 cm/s. Diameter = 2.21 cm; 4225 cc/min.

LA pressure in systole: $4 \times (4.6)^2 = 85$; arm blood pressure = left ventricular (LV) systolic pressure = 123 -pressure drop = 123 - 85 = 38 mm Hg; the Swan-Ganz wedge pressure was 23 mm Hg (however, on other traces the calculated Doppler LA pressure was also 23 mm Hg).

Figure 3. Same as Figure 2, except at 100 mm/s velocity. Note the bigeminy.

Figure 4. Honeywell (Biosound Corp. Indianapolis, Ind) Pulsed Wave Doppler (PWD) freeze-frame tracing, from the apical 4-chamber view, with the sample volume (SV) in the LV inflow tract (LVIT) or mitral outflow. Peak V, initial (D) = 2.16 m/s, end-diastole (A) = 1.6 m/s. Diastolic gradients: end - $4 \text{ V}^2 = 10 \text{ mm}$ Hg, maximal $4 \times (2.16)^2 = 19 \text{ mm}$ Hg. There is a rapid early slope, and the pressure half-time is only 38 ms.

Figure 5. Honeywell PWD, from the apical 4-chamber view, with the SV placed in the LA. The regurgitant flow, systolic negative away from the transducer, has a peak V of 80 cm/s. The forward velocities, diastolic positive toward the transducer, have a peak V of 70 cm/s.

Calculation of a mitral valve regurgitant fraction is not accurate, because determination of mitral valve area and the area through which the jet passes in MR, have not yet been satisfactorily solved.

Subsequently, an incomplete cardiac catheterization revealed a PA pressure of 66/20, mm Hg, a wedge pressure of 15 mm Hg. mean, and no significant mitral valve gradient! But the LV was never entered at the study.

Discussion

In doppler echocardiography of MS may, the apical 4-chamber view is the best, with the transducer directed backward, medially and superiorly. A separate Doppler transducer is more sensitive. The SV is placed in the LVIT

(mitral). The left parasternal position is another choice. Attempt multiple windows parallel to the jet, and choose the maximal velocities with the highest frequencies and narrow bands. The patient is often in the left lateral position. Short sharp valve clicks may be heard. For combined mitral stenosis and regurgitation in an adult, and greater depth of the mitral orifice, both the 1 mhz frequency and the range ambiguity may be necessary to obtain the increased forward flow velocity and the high V in the regurgitant jet. The doppler echo may reveal:

- 1. Increased V of diastolic flow in mitral orifice, usually > 2-3 m/s; the maximal V is located in the jet. The normal adult peak V is 0.9 M/S (0.6-1.3), and 1 m/s (0.8-1.3) for children, and rapidly declines during the diastolic filling period, with a second usually smaller positive wave with atrial systole. A significant pressure drop is present throughout diastole, from a maximal V of over 2 m/s it falls slowly and then increases at end-diastole with atrial contraction to > 1 m/s. These all depend upon compliance.
- 2. The mitral pressure gradient (P) can be determined from velocity as $P_1 = 4V^2$ (Modified Bernoulli equation). If V_1 is not high it can be ignored. High flow states can elevate velocities proximal to the valve and lead to gradient overestimation unless V_1 is squared and subtracted from V_2^2 . In MS, V may be > 2 m/s and gradients > 16 mm Hg. and depending on the range-velocity product, induce aliasing on the PWD. Pressure drop depends upon the varying diastolic cycle lengths.

3. Diastolic spectral broadening or disturbance of flow; the degree and duration are related to the severity.

- 4. A characteristic flow profile with decreased and prolonged slope of curve, which is plateaued or flattened (comparable to the decreased E-F slope of the M-mode echo in MS).
- 5. Alterations in configuration of velocity curves occur, including: indentations and notches, of D wave from flow disturbances (the normal curve is smooth and biphasic): mild MS-biphasic; incrased late diastolic peak, A wave >D wave (this occurs also with decreased LV compliance and increased end-diastolic pressure); moderate MS-monophasic, peaking in mid and late diastole; irregular and dome-shaped; severe MS-reduction in size or loss of a wave; very turbulent with a slow steady ascending flow and a sharpe descent at end-diastole.

6. The audio signal- high frequencies, uniform, pure pitch.

- 7. Aortic flow V curve may show a lower V and a slower increase in V, a rounded form and peak V later in systole.
- 8. In the presence of atrial fibrillation the second D wave is not present, and in the presence of LV hypertrophy a great augmentation in V follows atrial contraction.
- 9. With high cardiac output and increased flow across the mitral valve as present in MR and left-to-right shunts, the diastolic flow across the valve during peak velocities may be heard as frequent repeated valve movements.
- 10. Mitral pressure half-time. This is defined as the time in ms it takes for the mitral velocity curve to drop to

one-half its initial peak value, or the time between V_{to} (initial peak diastolic V) and V_{11/2} (diastolic half V), or the time required for the initial V (V₀) to fall to a value equal to the V divided by the square root of 2 (1.41): $V_{11/2} = \frac{V_{10}}{\sqrt{2}}$ It is related directly to the mitral orifice area. Values: normal 20-60, mean 46 ms. MS 90-383 mS (mild 100 ms, moderate 200 mS, severe 300-400 mS or more-Hatle). 100 ms yields a valve area of 2 cm² and a time >220 ms predicts a < 1 cm² valve area. The pressure half-time is independent of mitral flow, cardiac output and heart rate, whereas the velocity and gradient are dependent (such as a gradient due to flow rather than to obstruction), and thus may help to distinguish MR from MS, and different severities of MS in which slopes may be similar. Tachycardia or a long P-R interval may preclude its measurement. MR or predominant MR may produce an augmented flow, velocity and gradient, as in this patient, but it possesses a rapid descent and short transmitral pressure half-time; measure V₁. A low flow may lower the gradient even in severe MS. Exercise decreases the pressure half-time.

11. Estimated mitral valve area (MVA) in cm² =

Pressure Half-time in ms.

12. Differential diagnosis: Other lesions which must be differentiated from MS in addition to MR are: a. Ventricular septal defect-increases mitral flow and V; b. Aortic regurgitation also produces high V jets into the LV in diastole; the V patterns, timing and beam directions are different; c. Left atrial myxomas obstructing the mitral orifice, induce high flow Vs and low frequency sounds in the LA and LV at beginning and end of diastole, before S₁ (tumor plop) different from valve clicks, prominent mitral valve flutter during diastole, disturbed flow in the LV and velocity curve deflections. CWD and PWD were applied from the apical and suprasternal notch positions.

Two-dimensional echocardiography has been useful in the evaluation of mitral valve disease, but it is limited in certain patients and in post-commissurotomy patients. PWD aliasing errors in high V jets (>2 M/S), artifacts and transducer angling effects limit Doppler methods. However, in MS and MR Doppler echocardiography has shown high sensitivity, specificity and predictive value, and excellent correlation with mitral valve gradients from cardiac catheterization. Doppler combined with two-dimensional echo offers the best noninvasive evaluation of mitral valve disease.

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MEDICAL ASPECTS OF NUTRITION

The Calcium-Blood Pressure Hypothesis: Evidence for Its Validity*

Njeri Karanja, Ph.D., R.D.** David McCarron, M.D.**

The Calcium-Blood Pressure Hypothesis: Evidence for Its Validity

Calcium plays a prominent role in a variety of physiological systems. The earliest clue that dietary calcium was predictive of cardiovascular risk was made about 25 years ago.^{1, 2, 3} Since that time, evidence linking calcium to blood pressure regulation has accrued in the form of epidemiological, experimental and a limited number of clinical trials.

Although mechanisms governing calcium's modulation of blood pressure remain ambiguous, it is becoming increasingly clear that calcium is a major contender among other nutrients for the dietary management of essential hypertension.

Essential hypertension is primarily a genetic disorder that requires environmental impact for expression. Ionic abnormalities involving mainly sodium and calcium have been documented in cells of hypertensive patients and their offspring, in cells of genetically hypertensive animals and in those women whose pregnancies are complicated by preeclampsia. Depending on an individual's level of exercise, body weight, smoking habits, level of psychological stress or dietary habits, these defects may eventually manifest themselves in the form of elevated blood pressure.

Dietary components that have been implicated in the etiology and/or management of hypertension include sodium, chloride, potassium, calcium, magnesium, protein, fats, calories and alcohol. Among these, sodium has been studied to the greatest extent. An impressively large body of data exists to support the contention that sodium intake is positively associated with blood

pressure. This association, however, has not always been demonstrable, leading researchers to postulate that some forms of essential hypertension —probably 30%—50%—are dependent for their expression on sodium intake. A relatively new concept appears to point toward a "calcium-sensitive" form of essential hypertension. A brief review of the evidence supporting this concept is provided here.

Epidemiological Evidence

Associations between dietary calcium and blood pressure were initially provided by investigations relating malnutrition to pregnancy. East Indian women receiving a supplement containing 440mg calcium per day exhibited lower incidences of gestational hypertension.⁴ This response was thought to be due to an improvement of general nutrition associated with supplementation. Later, however, a similarly low incidence of preeclamptic hypertension was reported prevalent in societies with suboptimal intakes of most nutrients except calcium.^{5, 6}

Studies in osteoporosis have lent further credence to the calcium "sensitive"-blood pressure hypothesis. Thirty-seven percent of osteoporotic women have been shown to have elevated systolic and diastolic pressures compared to only 15% of non-osteoporotic women.⁷ Even though bone demineralization in osteoporosis is a complex process involving a variety of factors, it is generally accepted that calcium deficiency accelerates bone loss. Suboptimal intakes of calcium may also be responsible for higher blood pressure values observed in men. Hypertensive males have been shown to have a lower rate of dairy product consumption compared to their normotensive counter-parts (approximately 70% of all dietary calcium consumed in the United States is derived from dairy products).⁸, ¹¹

Perhaps the strongest epidemiological testimony for the calcium hypothesis comes from the analysis of large health data bases within mainland U.S. and Hawaii.^{9, 10, 11, 12}

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In a recent analysis of the Health and Nutrition Examination Survey (HANES I), dietary calcium was identified as the nutrient that had a significant, consistent and independent association with blood pressure among a sample of previously undiagnosed hypertensives. An independent evaluation of the same data base with a slightly different analytical approach yielded the same information, as did the analysis of two other large data bases. As a significant control of the same information, as did the analysis of two other large data bases.

Evidence from Animal Experiments

Associations suggested by epidemiological investigations have found confirmation in experiments involving animals. Marginal intakes of calcium raise blood pressure in normal¹³ and pregnant¹⁴ rats, while supplemental calcium decreases blood pressure in these same animals.¹³, ¹⁴

Calcium's actions are manifested to the greatest extent, however, in animals where several abnormalities of calcium metabolism accompany hypertension. These abnormalities include renal calcium wastage, decreased ionized serum calcium values, elevated parathyroid hormone levels and impaired calcium absorption.^{17, 18, 19, 20} These abnormalities have been documented in mineralocorticoid-induced hypertension, 23 in genetic hypertension of the New Zealand strain¹⁹ and in the spontaneously hypertensive rat (SHR). 15, 16, 20 In the SHR, supplemental calcium not only prevents a rise in arterial blood pressure in the young animal, but will reverse established hypertension in the adult rat.²¹ Interestingly enough, total exclusion of calcium from the diets of very young (five-week-old) SHRs results in an initial rise in blood pressure up to seven weeks of age, at which point they stabilize to near normal values. This bimodal response to calcium deprivation is presumed to be due to an initial rise in parathyroid hormone (PTH), which in turn increases vascular smooth muscle tone and consequently blood pressure. After the seventh week, continued calcium deprivation no longer evokes enhanced PTH production, which results in a decrease in vascular tone followed by attenuation of hypertension.22 Later, growth retardation resulting from calcium deprivation may account for the lower blood pressures.

Some interactive aspects of calcium metabolism with that of other nutrients and the effect of such interactions on blood pressure regulation have been partially investigated. Calcium's hypotensive effects appear to be compromised when high amounts of protein,²³ chloride,²⁴ and parenteral phosphate²⁵ are introduced into the diets of SHRs. Nutritional consequences of increasing calcium for purposes of alleviating hypertension have as yet to be evaluated.

Evidence from Human Experiments

Few studies have evaluated the effect of calcium on blood pressure regulation in humans. Nevertheless, the inquiries have yielded remarkably similar results despite divergent methodological approaches. More importantly, most of the trials have used non-pharmacologic doses of calcium that theoretically could be achieved through dietary means. In a parallel trial of placebo versus one gram of calcium per day, young normotensive adults experienced blood pressure reductions of 6% by the eighth week of the trial when compared to the placebo group. 26 Blood pressure reductions of a similar magnitude were achieved in normal pregnant women receiving either 1 g or 2 g elemental calcium when compared to a group receiving a placebo. The 2 g supplementation appeared to prevent the characteristic elevations of blood pressure observed in the third trimester of pregnancy. 27

To date, two groups have reported trials involving patients with essential hypertension. Calcium loading in ten patients with essential hypertension produced significantly lowered blood pressures after days of supplementation. The hypotensive effect of calcium appeared to have a synergistic link with low plasma renin activity²⁸ and, in a second report by the same researchers, with vitamin D supplementation.²⁹

The first randomized, double-blind, placebo-controlled, crossover trial of calcium as therapy for mild to moderate essential hypertension has recently been reported.³⁰ In that study, 48 hypertensives and 32 matched normotensives received either 1 g calcium per day (as the carbonate salt) or placebo for eight weeks. After a washout period of four weeks, treatments were switched for an additional eight weeks. Compared to placebo, 1 g calcium per day significantly reduced average systolic blood pressure by 6-7 mmHg and average diastolic blood pressure by 3 mmHg in hypertensive patients. It was noted that reductions in blood pressure were not apparent until after the sixth week of supplementation and were still declining when therapy was discontinued.

As with any trial, some of the individuals in this study did not respond to therapy. Using a 10 mmHg or more drop in systolic pressure as criterion for response (a standard often used to evaluate the effectiveness of hypotensive drugs), participants in this study were classified as either responders or nonresponders. Systolic blood pressure was chosen since it is thought to be a better physiological marker for smooth muscle tone. Smooth muscle tone is the component of blood pressure regulation that is most responsive to calcium manipulations. When this criterion was adopted, it was noted that 44% of the hypertensives and 19% of the normotensives reduced their systolic blood pressure by an average value of 21 mmHg and diastolic pressure by 7 mmHg.

Taken collectively, these data provide strong support for the "calcium sensitive"-blood pressure hypothesis. Yet, a number of issues must be addressed before firm therapeutic guidelines can be formulated. Future research must compare the value of calcium obtained entirely through dietary means to that provided in pill form, i.e., are they equally effective in lowering blood pressure and if so, what doses are desirable? Furthermore, it will be important to determine whether alterations in calcium intake require concomitant alterations in nutrients, such as vitamin D and phosphorus, that are physiologically linked to calcium. The nature of interactions of calcium with other nutrients and/or drugs used to manage hypertension, as well as its interaction with other environmental factors such as stress, needs clarification.

Only when these concerns are addressed and independently evaluated by different laboratories can any meaningful alterations in dietary habits be recommended.

Summary

The calcium-blood pressure connection can no longer be considered a mere chance association. A causal relationship has been postulated based on studies in animals and in clinical human studies. However, more research in the role of calcium from dietary sources, its interaction with nutrients and drugs, as well as its comparative biovailability and desirable intakes, will have to be done before any therapeutic or preventative recommendations can be made.

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What can you do for hypertensives like Mary B?

Uncontrolled

Moderate hypertension (160/110 mmHg) with recent increases despite medication.

Overweight

At 73 largely sedentary... weight even more of a problem now.

Forgetful

Misses appointments and frequently fails to follow instructions.

Coexistent diabetes

On daily insulin after diet, exercise, and oral agents failed.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

.

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Mary B represents 2,165 women over 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians:

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Mary B's difficult age group?

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Use in diabetes

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta-blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.³⁶

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁷ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy!

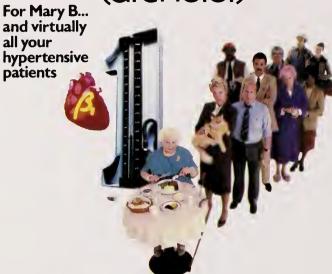


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DESCRIPTION: TENORMIN* (atenofol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-{2'-hydroxy-3'-{1-methylethyl} amino} propoxy}. Atenofol (free base) has a molecular weight of 266 ft its a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freefy soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chlorotorm (3 mg/ml at 25°C) in the case of the compound of the compoun

sion it may be used alone or concomitantly with other antinypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously Both digitalis and atenoloi slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it withdrawal symptoms occur.

should be advised to limit physical activity to a minimum TENORMIN should be reinstated it withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy Initiated
at 50 mg and a beta,-stimulating agent (bronchodilator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia if freatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and frichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg., dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg., profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I/V.)

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyroloxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg., fachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION)

Drug Interactions: Catecholamine-depleting drugs (eg., reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and o'r marked bradycardia which may produce verigo, syncope,

of clonidine.

Carcinogenesis, Mutagenesis, Impalrment of Fertillity: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose fevels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or fremale rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atendol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atendol (starting af 15 mg/kg/day or 7.5 times the maximum recommended

human dose) and increased incidence of afrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolof/kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more firmes the maximum recommended human dose. Although similar effects were not see
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 firmes the
maximum recommended human dose. There are no adequate and well-confrolled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the

potential risk to the fetus

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

atenciol
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by fine patient (U.S. studies) or elicited (eg. by checkfist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-freated patients than when these reactions were volunteered. Where trequency of adverse effects for TENORMIN and placebotectuals relationship is uncertain. is similar, causal relationship is uncertain.

these reactions were volunfeered. Where trequency of adverse effects for TENORMIN and placeby is similar, causal relationship is uncertain. The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%). The properties (0%-0.5%), light-headedness (1%-0%), irredness (0.6%-0.5%), latigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS). wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), diredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), foreaming (3%-1%)
GASTROINTESTINAL: diarrhea (3%-29%), nausea (3%-1%)
RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Disconfiniance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored toffowing cessalizing at health and considered if any such reaction is not otherwise explicable. Patients should be closely monitored toffowing cessalizing at health and considered if any such reaction is not otherwise explicable. Patients should be considered if any such reaction is not otherwise explicable.

be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENDRIAN JOHANNES.

with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiration y distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time an place, short-term memory loss, emotional fability with slightly clouded sensorium, decreased pe formance on neuropsychometrics.

Gastrointestinal: Mesenteric afterial thrombosis, ischemic colitics.

Characteristic alongeria, Peviropio's disease enghematous rash, Pavingurd's phenomenon.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolor reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension

on emergency freatment of overdosage is available. The most common effects expected with over dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotensio bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circuitation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted: Bradycardia: Atropine or another antichofinergic drug. Heart Block (Second or Third Degree): Isoproterenof or fransvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or not epinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Ammonphyline, soproterenol, or atropine. Hypoglycemia: infravenous quicose. DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks if an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any turther benefit. TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type duretics, hydralazine, prazosin, and alpha-methydopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mf/min/1 73 mf (normaf range is 100-150 ml/min/1.73 mf), therefore, if following maximum dosages are recommended for patients with renal impairment:

Atenolof Efimination Half-life Creatinine Cfearance (ml min /1 73 m²) Maximum Dosag (hrs) 16-27 >27 50 mg daily 50 mg every other t 15-35 < 15

Patients on hemodialysis should be given 50 mg affer each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets w Stuart embossed on one side and NDC No. 105 embossed on the ofher side are supplied in monthly calendar packages of 28 tablets, boffles of 100 fabrets, and unif-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolof) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 1 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled re temperature.

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Food Allergy and Food Intolerance*

John A. Anderson, M.D.**

A dverse reactions to foods and food additives may be broadly classified into two types: (1) immunologic reactions (food allergy) and (2) non-immunologic reactions (food intolerance).

Food allergy includes hypersensitivity reactions that are proved to be caused by or influenced by a food protein (allergens) via an allergen-specific immunoglobulin E. Immunoglobulin E (IgE) is a serum protein that mediates many common types of allergies besides food allergies, including hay fever, bee stings and penicillin hypersensitivities. Food allergy may also include other immune reactions.

Food intolerance is an adverse response to a food involving non-immunologic reactions (i.e., does not involve IgE). These include food poisoning and toxicity, anaphylactoid and other foodmediator release reactions. Food intolerances also include food idiosyncratic reactions, such as those caused as a result of genetically induced enzymatic deficiencies (e.g., lactose intolerance), pharmacologic (drug-like) food reactions and, finally, food reactions that affect the body metabolism.

Signs and Symptoms of Food Allergy

Most of the signs and symptoms of food allergy involve the skin (itching, erythema, hives, eczema, edema) or the gastrointestinal tract (vomiting, diarrhea, abdominal pain). In the case of systemic anaphylaxis, additional signs and symptoms may include the respiratory system (sneezing, wheezing), the eyes (conjunctivitis), and the cardiovascular system (palpitation, cardiac arrhythmia, shock collapse).²

Over the past 50 years, a school of thought has emerged suggesting that occasionally the symptoms of allergy can involve the nervous system, behavior and muscles and joints.² Thus, signs and symptoms, such as fatigue, hyperactivity, headache, anxiety, muscle and joint pain and arthitis, also have been attribute to food allergy.^{1,2,3}

Although debate in this area is likely to continue, when well-designed blinded studies have been performed, the relationship between these types of symptoms/signs and diet have not proved to be important.^{2, 4, 5, 6, 7, 8, 9} At this point in time, it is safe to conclude that in those patients presenting with either skin or gastrointestinal complaints (the sings more typical of allergy) and immunologic reactions to food (food allergy) should be considered. Patients with other symptoms are unlikely to be suffering from food allergy.

Incidence of Food Allergy

The exact incidence of all adverse reactions to foods is unknown. Food intolerance reactions, however, far outnumber the immunologic or food allergy reactions. True allergic reactions to foods are most common in infants, the greatest prevalence probably being among those children consuming cow's milk where the incidence may be 1%. Genuine food allergy reactions in adults are relatively uncommon.¹²

The literature on this subject may be confusing. Surveys among parents of small children have indicated that 5%-10% may have gastrointestinal complaints or skin rashes as a result of exposure to a a variety of foodstuffs.¹⁰, ¹¹ However, Bock, when studying the natural history of food allergy, found that if the offending food was avoided for a short period of time, many of the patients would not react when rechallenged.¹¹

In an older group of children with a past history of food allergy, May and Bock found, using double-blind food challenge (DBFC), that only one-third of the children could be proven to be food sensitive. When specific children who have documented allergic reactions to foods have been followed, some have been shown to regain their clinical tolerance to a specific food despite retaining positive skin tests to food extracts or the presence of food-specific IgE antibodies in the serum. One of the great difficulties in establishing true incidence figures, particularly in adults, relates again to the exaggerated reports of the various behavior neurological and somatic complaints related to diet.

Allergic Reactions of Food Allergens

According to May, about 90% of food allergic reactions as evidenced by DBFC are caused by a relatively few foods, including milk, eggs, legumes, tree nuts and wheat.^{2, 12} Recent experience utilizing DBFC in children with atopic dermititis have identified the same foods.¹³ Well-documented studies involving individual patients with anaphylactic sensitivity have implicated the following additional important foods: fish, seafood (particularly shrimp), and to a lesser degree, citrus fruit, melons, bananas, tomatoes, corn, barley, rice and celery.¹

Idiosyncratic Reactions to Food Additives

A number of food additives have been implicated in food intolerances but the evidence is inconclusive and several components continue to be researched. This includes tartrazine (yellow #5), sodium benzoate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), monosodium *L*-glutamate and sulfites. All of the adverse reactions associated with these food additives are believe to follow non-immunologic mechanisms.¹⁴

Tartrazine has been reported to induce bronchospasm

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^{**}Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202

in as many as 15%-60% of aspirin-sensitive asthmatics, in causing or exacerbating chronic urticaria in adults, and being responsible with other colors in causing hyperactivity in children. Despite Feingold's claim that 50% of children with hyperactivity would be helped by a diet devoid of colors and preservatives, it has been found that only a *few* children would be improved on the diet or show an adverse effect in a special learning test on color challenge (predominantly tartrazine).⁴

Although BHA/BHT and sodium benzoate have also been implicated, very little documented evidence relates BHA/BHT and sodium benzoate to either asthma, exacerbation or chronic urticaria. While Scandinavian studies report that food additivies are a major cause of chronic urticaria, studies in the United States have not verified this impression.¹

Monosodium glutamate is reported to be responsible for the "Chinese restaurant syndrome" (headache, facial flush and chest pain). There also has been a single report of monosodium glutamate causing bronchospasm similar to that seen in sulfite-sensitive individuals.¹⁵

The sulfites, such as sodium metabisufite $(Na_2S_2O_5)$, have been implicated in a new syndrome of acute onset bronchospasm, especially in known asthmatics, ¹⁶ as well as shock in some cases. The exact prevalence of these problems is not clear at time.¹, ¹⁴ However some investigators feel as many as 5% of all asthmatics could be sensitive. ¹, ¹⁴, ¹⁷, ¹⁸ Diets devoid of sulfites, however, many not improve the overall asthma condition.¹⁷ Finally, clinical challenges of suspected patients who react in a typical fashion after a restaurant meal often do not confirm a sensitivity to sulfites, indicating that other factors may be involved.¹⁹

Diagnosis of Suspected Food Allergy

The history of the events surrounding the adverse reaction to the ingestion of a food is the most important aspect of diagnosis. 12, 20 The history may give clues to help separte those issues that are probably nonimmunologic in nature from those immunologic or allergic reactions. The mainstay of simple office diagnosis in the investigation of allergic reactions to foods is the use of a standard elimination diet devoid of the more common allergic foods (see Allergic Reactions to Food Allergens). The diet is administered for a period of time (two weeks) and is followed by a step-wise, open challenge of single foods added back to the diet over a three- to seven-day period.^{1, 12, 20} For those cases requiring confirmation of the history and open challenge, the DBFC procedure under controlled conditions can be used to verify the relationship between the food or food additive and the symptom complex. Even DBFC has its drawbacks.2 Food challenge in this manner is not recommended in the case of systemic anaphylaxis because of the risk of the procedure. The results of DBFC do not indicate the mechanism of the adverse food reaction. Finally, since the DBFC procedure is done under "unnatural" conditions all "negative" food challenges should be confirmed by subsequent open challenges.²⁰ In the case of suspected sulfite-, tartrazineand monosodium glutamate-induced bronchial asthma,

oral challenge of the suspected food additive can be evaluated using serial pulmonary function testing as an end point.

In food allergy problems, supplemental information concerning the mechanism of reaction can be obtained by the use of immediate-reacting (IgE) prick skin testing, the allerge-specific radio-allergosorbent test (RAST), or an enzyme-linked immunosorbent assay (ELISA). Prick skin testing may be helpful as a screening test to predict which foods the patient has developed an immunoglobulin E-mediated sensitivity.¹³ A positive prick test to a food extract can be verified clinically by DBFC in approximately one-third of the cases, whereas a negative food prick test almost always is associated with a negative DBFC. Other immunologic tests may be helpful. The leukocytotoxic test and subcutaneous/sublingual and provocative techniques have been shown in several studies to be unreliable indices of adverse food reactions.1, 21

Treatment of Food Allergy

The principla treatment for all adverse reactions to foods is avoidance. Following investigations to identify the offending food, the specific food should be either completely eliminated from the diet or avoided to such an extent that clinical symptoms are not a problem. In the case of systemic anaphylaxis to a food, it is often advisable to supply the patient a preloaded syringe of epinephrine (HCL) in case the patient has a reaction to an unrecognized food. Oral experimental lactose-free cromolyn sodium and corticosteroids may be hopeful in some allergic gastrointestinal disorders and in Heiner's syndrome.¹

Available data suggests that it is possible to prevent allergic sensitization in potentially susceptible infants if cow's milk and some solids are withheld from the diet of the infant born to allergic parents.^{1, 10} It also may be important to eliminate potential allergic foods from the mother's diet in the last stages of pregnancy as well as during the time when she is breast feeding.

Subligual neutralization treatment has been advocated by some physicians as beneficial in the management of food allergy, but these claims have largely been disrupted. Classic allergen immunotherapy has not been shown helpful in the management of the usual food allergic patient. The Feingold diet may be safe to use in the management of hyperkinesis, but the expectation for success should be limited.⁴, ²¹

Summary: Adverse reactions to foods and food additives include those that involve an immune mechanism of reaction (food allergies) and those that are non-immunological in nature (food intolerance). The signs and symptoms of food allergy usually involve the skin and gastrointestinal tract and are "classic" allergic symptoms. Classic food allergy is more likely to occur in children. Food intolerance occurs more frequently at all ages. A number of food additives have been implicated in food intolerance, as none involve an immune mechanism of reaction. The role of food additives in food intolerance is not well established in many cases, has been discounted in others and continues to be the subject of current research. Although the history of events

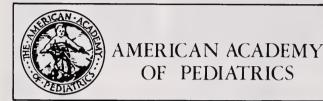
concerning an adverse reaction is important and gives clues to the specific type of problem (food allergy versus food intolerance), confirmation of the reaction is sometimes desirable. The can be done either by use of a standard elimination diet of non-allergic foods, followed by open challenge or by DBFC for more difficult situations. Food allergy skin testing and other in vitro immunologic tests may be helpful as supplemental information in those cases where food allergy is suspected. The best treatment for an adverse reaction to food is avoidance. Unproven and unapproved diagnostic (e.g., leukocytotoxic test) and therapeutic techniques (e.g., sublingual neutralization) are not recommended in food allergy management.

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MEDICAL SPECIALTIES NEWS



SUDDEN INFANT DEATH SYNDROME REMAINS MYSTERY: VACCINE NOT THE CAUSE

"Although the entire medical community hopes the cause of Sudden Infant Death Syndrome (SIDS) is soon detected, there is still no answer to this tragedy," said Robert J. Haggerty, M.D., president of the American Academy of Pediatrics (AAP). "What we do know, however, is that the pertussis vaccine —as well as any other childhood immunization— is not the cause of SIDS, or infantile apnea."

Haggerty responded to a recent ABC television broadcast which implied that one of the routine childhood immunization, DTP which protects against diphtheria, tetanus and pertussis causes SIDS. Although the cause of the SIDS is not known, a major nationwide research study has shown that the DTP vaccine is not a factor, Haggerty said.

The research, administered by the National Institute of Child Health and Human Development (NICHD), was a multicenter, cooperative study designed to examine all possible causes of SIDS. The study carefully examined all the evidence that might link the pertussis vaccine to the syndrome.

The findings, reported late in 1982 by the Department of Health and Human Services (HHS), indicated not only that there is no evidence between the vaccine and SIDS, but that SIDS cases are less likely in infants who recently received the DTP shot. Haggerty said the study analyzed over 800 SIDS cases from all over the country.

Haggerty stated that it is particularly cruel that the TV show implied a link between the pertussis vaccine and SIDS when the NICHD study had been made available to them. "Parents who have lost infants to SIDS should not be additionally burdened with such misinformation," he added.

American Academy of Pediatrics News, Feb. 1985

CHILDREN'S SLEEP PROBLEMS MAY INDICATE DAYTIME STRESS

Common sleep problems in otherwise healthy children, such as bedtime struggles and night waking, can be an indication of more pervasive disturbances in the child, according to a joint study from Rainbow Babies and Childrens Hospital in Cleveland and Cleveland Metropolitan General Hospital.

In the study, published in the March issue of *Pediatrics*, mothers were asked about 17 potentially stressful events in their child's lifetime. The children with sleep problems experienced more stressful events than the children without sleep problems.

Specifically, sleep disturbances seemed to occur in children whose mothers had psychologically withdrawn from them, or had an accident or illness in the family. In addition, an unaccustomed absence of the mother during the day such as her return to work or school, the mother's depressed mood, or sleeping with parents also contributed to sleep problems.

Children with sleep problems had an average of three of these five situations, while children without sleep problems averaged only one of the five. These situations, according to the researchers, were crucial identifying elements in the creation or continuation of sleep problems, as well as potentially important symptoms of a behavior problem if they lasted more than one month.

Sleep problems occur regularly in 20-30 percent of children up to age four. When the problems include conflicts such as protesting bedtime for more than one hour, waking parents many times during the night and refusal to allow parents to leave the room, this points toward stress in the child's own life or in his family life.

The study, which included 96 white children from six months to four years of age, found that 30 percent had a sleep problem that could be stress-related. The average sleep problem in the study lasted 12 months and occurred most often in children two to four years old.

The researchers note that sleep problems persisting for a lengthy time may warrant contact with a health professional to determine the nature of the child's stress and how to effectively combat it.

LOW BIRTH WEIGHT INFANTS HAVE VISUAL-MOTOR TROUBLES IN PRESCHOOL

Many low birth weight babies that have survived because of modern technology are now school aged, and pediatric researchers say that school performance is an early indication of how these children will function in society as they grow older.

In a study reported in the March issue of *Pediatrics*, researchers at Case Western Reserve University, Cleveland, and Cleveland State University, say that children who were very low birth weight infants had significant visual-

motor problems when compared with normal birth weight classmates at preschool.

The investigators studied 46 children of normal IQ that were part of the Rainbow Babies and Childrens Hospital High Risk Follow-up Program. All weighed less than 1500 grams (3 pounds) at birth. They discovered that the children scored significantly lower on spatial relations and visual-motor integration tests. An example of a comparison copying test, one done by a full-term, normal birth weight child and the other by a very low birth weight child, is attached.

In the study, supported by the Cleveland Foundation, the researchers stressed the need for early identification of possible learning disabilities and the implementation of programs to monitor and assist these children into the early grades to "prevent the compounding of these difficulties."

The mean gestational age of the children was 30 weeks, and the researchers suggested that because the final growth differentiation phase of the visual cortex occurs in the third trimester of pregnancy, this might provide a clue as to why the low birth weight children have visual-motor skill problems.

The low and normal birth weight children had similar demographic backgrounds and both groups were evaluated at age five by a phychologist who was not familiar with their birth weights. The children's scores on other cognitive performance tests, such as picture vocabulary, memory and quantitative concept tests, were not significantly different.

AMERICAN COLLEGE OF PHYSICIANS



NOW, AN ADULT APPROACH TO VACCINATION: MEDICAL EXPERTS TO DISCUSS ADULT IMMUNIZATION AT MEDICAL MEETING

For the first time, medical experts concur on official recommendations for adult vaccines. Important issues still need to be resolved, however, including the cost benefits of immunization and how to increase the use of vaccines to better protect adults against disease.

These issues and state-of-the-art vaccine recommendations were examined in a symposium on adult immunization at the 66th annual scientific meeting of the American College of Physicians (ACP), in Washington, DC.

Pneumonia and influeza together are the sixth leading cause of death in the United States. Heaptitis B affects an estimated 100,000 Americans each year, leading to about 16,000 hospitalizations. "Although vaccines are available for these and other diseases, they are largely underutilized," according to David S. Fedson, MD, FACP, of the University of Virginia School of Medicine, moderator of the symposium. The reason, according to Dr. Fedson, is

that most physicians are trained to think in terms of treating, rather than preventing, disease.

The importance of immunizing adults only recently has been stressed by the medical community, in spite of the marked success of childhood vaccination programs. With the advent of new and improved vaccines that are effective against adult diseases, physicians must learn what vaccines can best protect their patients from unnecessary illness and death. Participants in the ACP symposium discussed current recommendations for seven key vaccines (tetanus, diphtheria, measles, rubella, hepatitis B, influenza and pneumococcal pneumonia) and examined patterns of actual vaccine delivery, the cost effectiveness of immunization and new vaccines on the horizon.



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AIRBORNE MEASLES CAN INFECT UNVACCINATED TOTS

A "super-spreader" of measles virus can contaminate the air of an entire room and cause airbone transmission of the disease, according to a report in JAMA. Reported is an autbreak of measles among children who visited a pediatrician's office in Muskegon, Michigan.

"The index patient was a 7-month-old Korean orphan who had developed measles with rash onset 16 days after arriving in this country," say Patrick L. Remington, MD, of Atlanta's Centers for Disease Control and colleagues from the CDC and public health offices in Michigan.

"Subsequently, four children, aged 4 months to 2-1/2 years, developed measles with rash onset 12 to 13 days after visiting the pediatrician's office." None had face-to-face contact with the index patient. Three arrived after the patient had left.

The facility of measles transimission has been debated for years, with prevailing thought favoring the idea the virus is transmitted only following face-to-face contact. That it can be transmitted by contaminated air opens new problems for control of the disease. Commenting editorially, Stephen C. Schoenbaum, MD, MPH, of Boston, points out, "Measles is a bad disease, frequently complicated by pneumonia, encepahalitis and death." Clearly, the elimination of indigenous measles is a laudable goal, he adds. "Yet it is unlikely that this will occur, given the possibility of airborne transmission, unless all children are immunized against measles at an early age."

The optimal time to immunize against measles is 15 months, but many children are not immunized until school age, when vaccinations are required. "That is clearly too late for some children who are still getting measles," Schoenbaum says. About 10 percent of measles cases now reported are due to importations, he adds. Visa-grating agencies notify families entering the United States that children must be immunized prior to entering school in hopes the children will be immunized prior to entering the country. Unfortunately, that doesn't always happen.

In the Michigan case, the researchers comment, "The first step to prevent transmission of measles in physicians' offices is to assure adequate immunizations of all patients and staff. None of the adequately immunized children present in the office around that time subsequently developed measles.

"Measures to specifically reduce the risk of airbone transmission include ensuring that there is adquate freshair ventilation in the office, respiratory isolation of all suspected cases, and seeing these patients without delay or at the end of the day."

JAMA March 15, 1985

AIDS VIRUS TRANSMITTED BY HETEROSEXUAL CONTACT

HTLV-III, the virus believed to cause acquired immune deficiency syndrome, can be transmitted by repeated heterosexual contact, according to a report in JAMA. Close household contact with persons who have AIDS or AIDS-related complex is not sufficient for transmission, the report adds.

Robert R. Redfield, MD, of Walter Reed Army Institute of Research, Washington, DC, and colleagues studied family members of seven married men who had AIDS or AIDS-related complex (defined by chronic lymphadenopathy and T-cell helper depletion). They found that five wives had evidence of HTLV-III infection, documented by the presence of virus and/or antibody. Three of these women also had symptoms of disease; the other four wives were clinically healthy. Of 11 children from these families, only one 14-month-old child was seropositive for antibody to HTLV-III.

The researchers suggest that the 14-month-old probably was infected with the virus from the mother at birth, since this is a known means of transmission and the mother had advanced clinical disease. The child had three unaffected siblings, and there were four other healthy children of parents who both had evidence of HTLV-III infection. "The lack of evidence of infection in the ten older children in this limited study suggests that close household contact between parents and children is not a significant mode of HTLV-III transmission," the researchers say. Commonly recognized risk factors were identified in only three of the seven male cases, the researchers note. Three men reported IV drug abuse, but none reported homosexual contact. Three more men reported heterosexual promiscuity, which has been recognized as a means of transmitting AIDS in Africa and in some other areas. The researchers add that recent data suggest that more than 30 percent of AIDS or AIDSrelated complex cases among military personnel are associated with heterosexual promiscuity as the sole risk factor.

The researchers say their study adds more evidence that heterosexual contact may be an important means of transmission of AIDS in the United States.

JAMA March 15, 1985

FAMILY HISTORY POSITIVE DOUBLES BREAST CANCER RISK

Women who have mothers or sisters who have had breast cancer are more than twice as likely to develp the disease than other women, according to a report in JAMA.

Richard W. Sattin, MD, and colleagues of the Centers for Disease Control, Atlanta, compared data from 4,735 women with breast cancer and 4,688 controls. "Compared with women without a family history of breast cancer, women who had an affected first degree relative had a relative risk of 1.5; and women with both an affected mother and sister had a relative risk of 14," the researchers say. First degree relatives are mothers or sisters; second degree relatives are grandmothers or aunts.

For women aged 20 to 39, 40 to 44, and 45 to 54 years, the estimated incidence of breast cancer per 100,000 attributable to first degree family history was 51.9, 115.1 and 138.6, respectively. The estimated incidence attributable to a second degree family history was 12.1, 19.2 and 92.4, respectively. The researchers also found that a woman's risk of breast cancer was greater if her mother or sister had unilateral rather than bilateral breast cancer and if the cancer and been detected at a relatively young age.

In a related article, J. Larry Hornsby, EdD, of the Medical College of Georgia, and colleagues report that informing patients of increased cancer risk may not result in psychological trauma. About 140 workers who were exposed to a chemical known to cause bladder cancer (Bnaphthyalamine) participated in three tests within four weeks of notification of increased risk: the Family APGAR, Impact Event Scale, and the Improved Readability Form of the Minnesota Multiphasic Personality Inventory. The tests were given again to 128 of the workers six months later, but the researchers found no evidence of excessive worry or psychological problems.

Commenting editorially, Mardi Horowitz, MD, of the University of California San Francisco, says Hornsby's results are reassuring, but evidence shows that response to such information varies among patients. Some patients are particularly sensitive to bad news, and when patients are reminded of risks frequently they may have higher levels of stress because denial is more difficult. When discussing risks for cancer or heart disease, Horowitz says physicians should watch for patients who may have severe reactions, and they should provide them with extra support.

JAMA April 5, 1985

PHYSICIANS TREAT, BUT DO NOT DIAGNOSE MENTAL DISORDERS

Physicians recognize and treat mental disorders much more often than they diagnose them, according to a report in JAMA. The majority of psychotropic drugs and "psychotherapy/ therapeutic listerning" provided to adults in office-based primary care occur during visits in which no diagnosis of mental disorder is recorded, reports Stephen F. Jencks, MD, of the National Institute o Mental Health in Rockville, MD. His observation comes from evaluation of data from the National Ambulatory Medical Care Survey.

"Patients who receive treatment without diagnosis tend to be older, established patients with established diagnoses who see the physician for a shorter visit and are more likely to have a follow-up appointment." Jencks says. The finding is not explained by a general tendency of surveyed physicians to record drug treatment without an appropriate diagnosis, nor is it explained by management of specific nonmental disorders with mental treatments, he adds.

"The data do not provide evidence as to whether mental treatment without mental diagnosis results from inadequacies in the current diagnostic system, inadequacies of physician knowledge and skills, or other factors," Jencks says. "Further clarification of this issue will require new research models."

He points out that despite growing agreement that the recognition of mental disorder by primary care physicians is important to good medical care, research to date has been inconclusive as to how regularly such recognition takes place and even as to how recognition should be defined.

The survey data show a rate of recognition of mental distress for adult visits in primary care settings at least double the rate of diagnosis of mental disorder.

"Primary care physicians recognize and treat a great deal of mental distress that they do not describe in the vocabulary of psychiatry. Whether the problem is in the vocabulary or in the physicians remains unclear," concludes.

JAMA April 5, 1985

CONFABULATION LIMITS LEGAL USE OF HYPNOSIS: AMA REPORT

Memories gained under hypnosis can involve confabulations and be less reliable than nonhypnotic recall, according to an AMA report published in JAMA.

"The use of hypnosis with witnesses and victims may have serious consequences for the legal process when testimony is based on material that is elicited from a witness who has been hypnotized for the purposes of refreshing recollection," says the AMA Council on Scientific Affairs report.

Not only is accuracy questionable, "but there is also the problem that hypnosis leads to an increased vulnerability to subtle cues and implicit suggestions that may distort recollections in specific ways, depending upon what is communicated to the subject," the report points out.

For these reasons, the AMA offers a number of

recommendations concerning the use of hypnosis in courtroom testimony:

- Hypnosis with witnesses and victims to enhance recall should be limited to the investigative process;
- Before using hypnosis, a psychological assessment of the subject's state of mind should be carried out and a detailed history of the individual's recollections obtained in a nonleading fashion. Informed consent should be obtained from the subject, if a decision of use hypnosis is made.
- Hypnosis should be conducted by a psychiatrist or psychologist skilled in clinical and investigative use of the discipline who also is a ware of the legal implications raised by use of hypnosis in the given jurisdiction
- Ideally, only the subject and practitioner should be present when the subject is hypnotized. Exceptions may be necessary, but they should be weighed against the risk of inadvertently cueing the subject.
- One free narrative recall should be elicited before hypnotic induction begins, regardless of procedures used.
- Subject response to termination of hypnosis and posthypnotic discussion about the experience are of major importance in assessing the experience.
- Further research should be conducted to help clarify the effects of hypnosis on recall, to enhance understanding of functional amnesias that affect witnesses and victims of crimes, and to shed light on the nature of normal and pathological human memory.

JAMA April 5, 1985

LESS BODY SWAY MARKS HIGH ALCOHOLIC RISK

People who sway less after three or four stiff drinks may be at an elevated risk for becoming alcoholics, according to a study in the April Archives of General Psychiatry. Marc A. Schuckit, MD, of the University of California, San Diego, Medical School, reports on a study of 34 young men with alcoholics in their families and 34 matched controls without alcoholic relatives. Following a dose of 0.75 mL/kg of ethanol (a measure of alcohol in relation to body weight), an increase in body sway was significantly less for those with alcoholics in the family than for controls. "A decreased intensity of reaction to ethanol should be explored further as a possible genetic trait market of a predisposition toward alcoholism," Schuckit says.

CARDIOVERSION CAN CAUSE SEVERE HEMORRHAGE

Use of electric-shock paddles to restore heartbeat in an infant can cause severe hemorrhaging, according to a report in the April Archives of Pathology and Laboratory Medicine. Joseph C. Parker, Jr., MD, and colleagues

from the University of Tennessee Memorial Research Center in Knoxville report autopsy findings of an eightmonth-old boy with severe cardiorespiratory problems. Resuscitation efforts with adult cardioverter paddles in an emergency room apparently caused hemorrhages throughout the spinal cord. "Use of adult cardioversion equipment in an infant may alter the amperage by decreasing resistance and, thus, create a potential hazard," they say.

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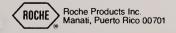
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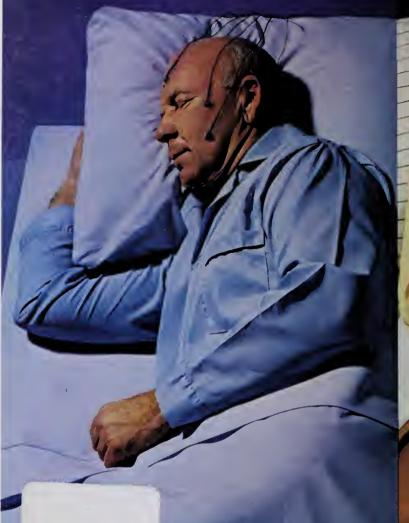
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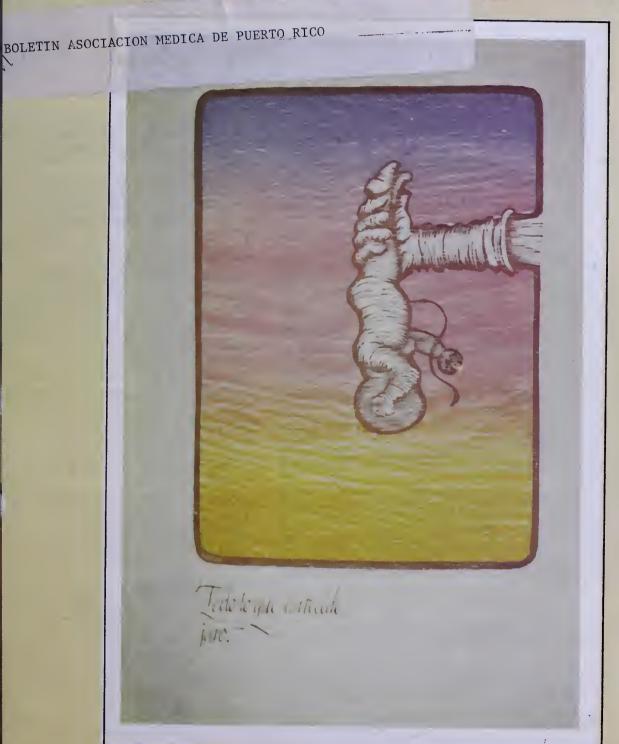
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La Junta Editora del Boletín de la Asociación Médica de Puerto Rico se siente muy complacida por el buen recibimiento que le han dispensado los Internos y Residentes al Boletín. Muchos dicen que habían "oido hablar" de la revista, otros que en alguna ocasión la "habían visto en la Biblioteca" o "en la oficina de un médico" y algunos cándidamente admiten que "desconocían su existencia". ¡Esto último a pesar de los ochenta años de publicación de la misma! Sin embargo, hay unanimidad en el sentido de que la mayoría leyó el número que se le envió, que el contenido del mismo les fue de provecho académico y que desean seguirla recibiendo. La Asociación Médica de Puerto Rico no escatimará esfuerzos para que nuestros Internos y Residentes continúen recibiendo y leyendo nuestro Boletín.

En este número cabe destacar el trabajo publicado por los doctores Carlos A. Pérez y Gloria Reyes de la Unidad de Cuidado Intensivo Neonatal del Hospital Pediátrico Universitario. Este artículo debe ser lectura obligada para todos los Pediatras pues de una forma muy ordenada y sencilla explican como diagnósticar, y las medidas iniciales a seguir por el "Pediatra Primario" en neonatos con el Síndrome de Hipertensión Pulmonar Persistente. Todos los que atienden neonatos conocen la frecuencia de aparición de este problema y lo importante que resulta el manejo apropiado para la sobrevivencia del niño.

El "Artículo Especial" sobre la enfermedad de Kawasaki, esperamos sea de provecho a nuestros lectores y ayude al mejor entendimiento de este enigma clínico.

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Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico

BOLETIN



NUESTRA PORTADA

El Recién Nacido. grabado del portfolio El Juramento de Hipócrates del artista puertorriqueño Antonio Martorell.

Nació en Santurce en 1939. Estudió Pintura en España con Julio Martín Caro y en Puerto Rico estudió gráfica con Lorenzo Homar.

Ha sido profesor de dibujo y grabado en la Escuela Nacional de Bellas Artes en México, en la Escuela de Artes Plásticas de San Juan, la Liga de Arte de San Juan y en la Universidad Interamericana de San Germán.

Entre sus obras más conocidas está Catálogo que obtuviera premios Internacionales en Puerto Rico, Alemania e Italia, y en la serie de dibujos Albúm de Familia que ha sido exhibida en Puerto Rico, Estados Unidos y México.

El Juramento de Hipócrates, es una serie de 10 grabados realizados por Martorell en 1980, en edición de 350 ejemplares caligrafiados individualmente con grabados en madera. Elabora el conocido Juramento en imágenes que describen el ciclo vital, aunado a una consciencia de la función social del médico. Las imágenes enfocan: la Mujer Embarazada, el Niño, el Adulto Trabajador; el Envejeciente Enfermo, la Muerte y el Recién Nacido. Este último fue escogido para la portada. El portfolio del Juramento de Hipócrates consta de 10 grabados firmados y enumerados por el artista. Puede obtenerse información adicional llamando a sus teléfonos 721-0656 ó 767-7875. El grabado del Recién Nacido que aparece en la Portada muestra la mano del médico sosteniendo al infante recién llegado a este mundo.

La Junta Editora agradece la cooperación y el esfuerzo del Dr. Miguel Colón Morales para lograr reproducir la obra del artista en nuestra portada.

EDITORIAL

Cartas al Editor

No creo que haya algún lector del Boletín que discrepe de mí al decir que nuestro Boletín se ha convertido en una revista médica de importancia cuya altura no había sido alcanzada anteriormente. La calidad científica de los artículos, las secciones de enseñanza y de informaciones varias, el uso correcto tanto del inglés como del español, la calidad del papel, la litografía y los infrecuentes errores tipográficos evidencian un adelanto notable. Prueba de esta mejoría es el endoso que está recibiendo de los anunciantes. Debido a estas entradas, el Boletín ha logrado, quizás por vez primera, autosuficiencia desde el punto de vista económico.

Sin embargo, a pesar de haber logrado ese nivel de excelencia, el Boletín adolece de UNA falta: las Cartas al Editor brillan por su ausencia. Esto da la impresión de que nuestra revista o no se lee o el lector no tiene interés en colaborar. La Sección no falta. La Sección existe. Lo que falta son las cartas, los comentarios, las críticas de los que la leen.

Para mí, de las revistas médicas que todavía leo, la Sección que me ofrece la instrucción más confiable y sobre la cual puedo fundamentar una opinión justa, es la de las Cartas al Editor. Es ahí donde se comentan o se cuestionan los métodos de investigación, los hallazgos, las deducciones y las conclusiones propuestas en artículos previamente publicados. Cuando se publican las cartas, éstas generalmente vienen acompañadas de una respuesta del autor u autores que incluye una explicación o un argumento en contra de lo criticado. De todo esto surgen polémicas muy instructivas, particularmente, para el lector.

Yo no puedo creer que los colegas que leen el Boletín están de acuerdo con todo su contenido. Debe haber por lo menos una discrepancia importante alguna vez. Nuestra profesión cuenta con investigadores, profesores y especialistas de talla, dotados con suficientes conocimientos y experiencia para atribuirse la autoridad que se requiere para señalar lo cuestionable o el hallazgo inesperado al cual se le debe dar énfasis. Obviamente, no estoy hablando de comentarios anodinos sobre tópicos triviales y de poco sentido. De recibirse, ya la Junta Editora se encargaría de discernirlos.

Confío en que estas líneas sirvan de acicate para aquellos miembros y no miembros de la Asociación Médica de Puerto Rico que, estando en desacuerdo con lo publicado, han guardado silencio, negándole al lector información valiosa y reveladora. Al Boletín le hace falta esa colaboración para que pueda cumplir su misión por entero. Espero que prontamente me den la satisfacción de ver en una edición próxima del Boletín la Sección que le falta: Cartas al Editor.

José W. Joursh ?

José M. Torres-Gómez, M.D., F.A.C.P.



PATHOLOGYReview

María Castillo-Staab, M.D.

Una mujer de 52 años, post-menopáusica presentó sangramiento vaginal repetido de seis meses de duración.

El examen ginecológico reveló un útero ligeramente aumentado de tamaño, parametrios y anejos normales.

El legrado uterino para fines diagnósticos reveló la lesión histológica de la figura 1.



Figura 1. Glandulas endometriales

¿CUAL ES SU DIAGNOSTICO?

- a. Mioma uterino sub-mucoso
- b. Adenocarcinoma del endometrio
- c. Adenomiosis
- d. Pólipo endometrial
- e. Hiperplasia atípica del endometrio

Departamento de Patología, Universidad de Puerto Rico, Recinto de Ciencias Médicas.

Hiperplasia de Endometrio

Terminología descriptiva de un desorden proliferativo de las glándulas endometriales manifestado por aumento en el número de las glándulas, anormalidades en la configuración arquitectónica de las glándulas y cambios celulares del epitelo de dichas glándulas.

La hiperplasia del estroma (tejido que rodea las glándulas) no se utiliza como criterio histológico para este diagnóstico. La patogénesis de la hiperplasia del endometrio se relaciona con: influencia exagerada del estrógeno, ciclos anovulatorios, disfunción ovárica, tumores productores de hormonas y estrógenos exógenos de terapia de sustitución.

El término clínico "dysfunctional uterine bleeding" cuyas siglas "DUB" se usan con suma frecuencia, se refiere al síndrome clínico que en muchas ocasiones se asocia al hallazgo patológico de hiperplasia endometrial cuando ocurre en mujeres de edad reproductiva antes de la menopausia muchas veces asociada a ciclos anovulatorios.

Los hallazgos patológicos que acompañan los ciclos anovulatorios representan lesiones de proliferación no secretora del endometrio y se deben diferenciar de la llamada hiperplasia genuina del endometrio que ocurre casi siempre en la menopausia o después de ella. Es considerada una lesión pre-maligna o precursora en la patogénesis del adenocarcinoma de endometrio y es precisamente la que presenta nuestro paciente.

Las variantes histológicas de hiperplasia endometrial se denominan: hiperplasia quística, hiperplasia adenomatosa e hiperplasia atípica del endometrio. Estas variantes corresponden a los términos de hiperplasia endometrial leve, moderada y severa.

Algunos autores consideran la hiperplasia endometrial atípica una lesión potencialmente maligna y para otros representa un carcinoma in-situ del endometrio. La hiperplasia quística se denomina también hiperplasia con patrón de "queso suizo", en ella las glándulas son redondas, dilatadas, tapizadas por un epitelio columnar alto y las mitosis son escasas. (Fig. 2) La hiperplasia adenomatosa produce un endometrio engrosado, algo polipoide y las glándulas aparecen de distinto tamaño con disparidad en la forma. (Fig. 3) El epitelio presenta estratificación y hay aumento de la actividad mitótica.

La hiperplasia atípica presenta glándulas irregulares, en número exagerado que se ponen en contacto entre sí. Las células epiteliales muestran atipia caracterizada por pérdida de la polaridad, hipercromatismo, nucleolos prominentes y abundante citoplasma eosinofílico. Las mitosis son frecuentes.

La importancia clínica del diagnóstico de hiperplasia endometrial depende obviamente del tipo histológico. El riesgo de asociar la hiperplasia quística con el desarrollo de carcinoma de endometrio es mínimo o no existente. Por el contrario el riesgo aumenta a 22% en los casos de hiperplasia adenomatosa y a 50% en los casos de hiperplasia atípica. Es por esto muy importante que el patólogo indique el tipo y grado de atipia en forma clara y concisa para así ayudar al clínico a planear su estrategia terapéutica.

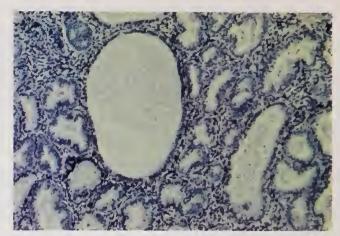


Figura 2. Hiperplasia quística del endometrio

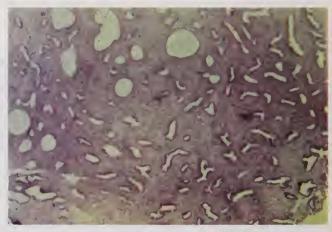


Figura 3. Hiperplasia adenomatosa del endometrio

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ESTUDIOS CLINICOS

Rehabilitation After Dialysis and Kidney Transplantation

L.H. Toledo-Pereyra, MD, Ph.D A. Schneider, MD S. Baskin, MD L. McNichol, MD K. Thavarajah, MD W.J. Lin, MD J, Whitten, MD

Abstract: The rehabilitation of end-stage kidney disease patients after transplantation was studied in a total of 106 recipients of 117 transplants. Fifty-three percent of our patients were employed. After transplantation, there was no significant increase in employment and only 17% were employed. This patient population did feel better, were less sick and physically more active after transplant in comparison to dialysis. Only 19% of our patients felt that they had "normal lives" during dialysis, whereas 40% felt so after transplant. There still was a significant number of patients (31%) who were sexually not functional after transplant.

The results after renal transplantation have improved. mainly due to the better understanding of the management of immunosuppressive therapy following transplantation. Patients with end-stage renal failure appear to be living longer with less complications after transplantation. However, it has not been clearly established how any of these patients regain their predialysis activities and employment status. There is a scarcity of material in the literature dealing with this question. This study examines our experience at our institution in an attempt to determine the real success in rehabilitating these patients after transplantation.

Materials and Methods

One hundred and six patients which received 117 transplants at Mount Carmel Mercy Hospital from September, 1979 to March 1982 were reviewed for this study. There were 21 patients which were not available for questioning, and thus were eliminated from the final analysis. Also, there were 21 patients whose kidney function was less than one month and these too were

eliminated from the study. Thus, we were left with 64 patients which involved 70 transplants. Most of our patients belonged to a high risk category. The distribution of male to female was 38 to 26 and the ratio of black to whites 37 to 27.

Each patient was carefully surveyed as to their past and present employment status and activity schedule. We analyzed the differences between pre-dialysis, dialysis and after transplant along the following guidelines. Table I shows our classification of employment, which is divided up to include full-time employment, part-time, or unemployment. If patients were unemployed we divided this further to distinguish those who were disabled and those able to work. The remainder of the employment status included housewives and students. For house wives we have divided this classification into those individuals capable of doing all the work, those who required help and could only do a certain amount and finally those who could do nothing.

The activity classification as also seen in Table I, was divided into normal activity, part-time normal, those who could only take care of themselves but do no more than this and finally those patients who needed assistance in taking care of themselves and those who were institutionalized. We also questioned these patients, where possible and appropriate, about their sexual function during these three phases of their lives.

Statistical comparisons of the rehabilitation data after dialysis or transplantation were done using Chi-square analysis.

TABLE I

Employment Criteria

Full Time Part Time Unemployed Disabled Housewife Student

_ Activity Criteria _

Normal
Part Time Normal
Self Care
Needs Help With Self Care
Institutionalized
Sexual Function

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Classification of patient employment and patient activity

Results

Of the total 117 transplants, the one-year actuarial graft survival was 59%. The average follow-up was 9.2 months, the range being 1 to 33 months. Of the individuals surveyed, 14 of 64 were diabetics. Education of those surveyed showed 4 patients with education of 0 to 8 years, 39 patients with 9 to 12 years, and 21 patients with greater than 12 years of education. The average age was 38 years with a range of 13 to 70 years. Most patients had dialysis prior to transplant for varying intervals of time, ranging from two weeks to five years. Only five patients had no dialysis prior to transplant. Twenty percent of our patients had to return to dialysis after rejection. Eighty-three percent of the patients on dialysis complained of some ill feeling, usually nausea, vomiting, feeling tired or weak. These symptoms resolved in all of these after transplant.

Figure 1 shows the full-time employment record of our patient population. Fifty three percent of the patients were employed full-time prior to renal failure. This percentage dropped to 15% while on dialysis and increased insignificantly (p>.50) to 17% after transplant. If we add those patients who are employable but unemployed, this increases the number of patients to 33%.

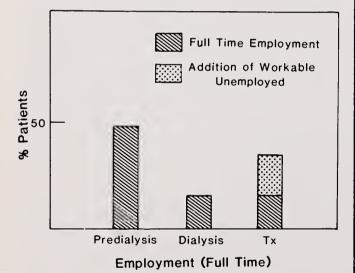


Figure 1. Fulltime employment of the entire patient population surveyed during predialysis, dialysis and after transplantation. We have included those patients employable but unemployed after transplant. There was no increase in employment after transplant.

We then divided the employment data further by looking at only those employed prior to renal failure. Of these 35 patients there is no significant difference (p>.50) between the number employed during dialysis (27%) and after transplant (29%). (Figure 2) Of those patients who were unemployed prior to renal failure 100% were still unemployed after transplant.

Taking into consideration the educational background, we see in Figure 3 that those patients with 9 to 12 years of education, 46% were employed prior to renal failure and this decreases to 7.6%, while on dialysis and decreases further to 2.5% after transplant (p>.50). Twenty-four

percent of these patients are housewives and these were eliminated from the above figures. For those patients with greater than 12 years of education 76% were employed prior to dialysis, 33% while on dialysis, and then this increased to 47% after transplant (p>.50). There were only 4 patients who had less than 9 years of education, 2 of which were housewives and 2 who were unemployed throughout the study.

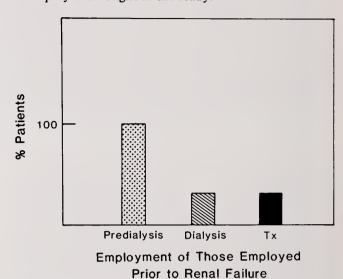


Figure 2. Full time employment during the study periods of those patients who were employed prior to renal failure. Again there is no increase in employment after transplant.

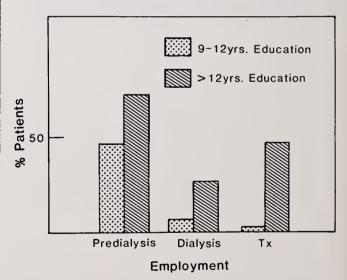


Figure 3. Full time employment during the study periods in relation to education. There is higher unemployment as the amount of education decreases; and no improvement after transplant.

All patients were graded according to their activity and a number value was given to each level. These number values were then averaged and presented here. Normal activity was designated as 9-10, part-time normal, 7-8, able to perform self-care, 5-6, need for help in taking care of oneself, 3-4, institutionalization was given 1-2 points. Figure 4, shows our results, 90% of our patients had normal activity prior to renal failure, this dropped to 19%

during dialysis and significantly increased to 53% (p<.001) after transplant. Seven percent of our patients were part-time normal initially, and this increased to 40% during dialysis and then decreased to 35% after transplant. A similar pattern was seen with the other patient activity levels.

There were 30 patients from whom information was available about their sexual activity and function. Women complained of reduced desire, while on dialysis whereas the men were either impotent or they too, lacked desire. Figure 5 shows our findings in this area. One hundred percent had normal sexual function prior to renal failure, whereas only 17% were normal during dialysis and 45% had no function at all. After transplant, 40% thought they were back to normal (p < .005) whereas 31% (p > .25) of the patients had no function at all.

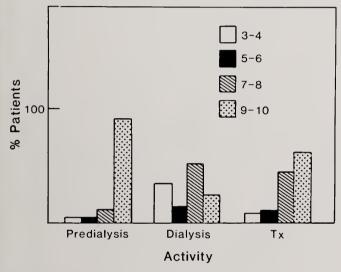


Figure 4. Activity of patients during the study periods. Each level of activity is plotted individually throughout predialysis, dialysis and after transplant.

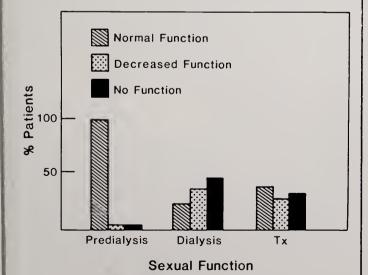


Figure 5. Sexual function during the study periods. There was improvement after transplant, but still a significant number of patients had no function.

For those patients labeled as housewives, a similar pattern of activity over the study period was seen. Figure 6 shows that 82% of the women felt they were normal prior to renal failure, whereas only 18% could do housework alone during dialysis. Fifty-five percent needed help and 27% could do none at all. After transplant a significant number (64%, p<.001) felt they could do all their work and activities but only 29% felt they were completely back to normal, twenty-seven percent needed help and 9% could do no work after transplant.

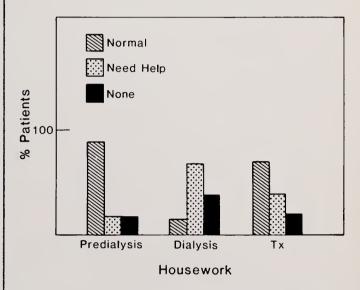


Figure 6. Activity of housewives during the study periods. Many women were more active after transplant than during dialysis.

Discussion

Although the technical results of transplantation have improved, very few authors have dealt with the question of rehabilitation of transplant patients. From our results we have tried to provide some insight into the problem.

In our study we were able to see various responses depending on the function of the transplanted kidney. Those patients who had poorly functioning transplanted kidneys or non-functioning kidneys, their lives consisted of a continual hospitalization until the kidney was totally rejected and then returned to dialysis. Other patients who had kidneys which lasted for long periods of time with occasional rejection episodes seem to be doing better than when on dialysis.²⁻⁴

From our results, we see that the number of patients employed after transplant is no greater than the number while on dialysis. In fact, the patients who are employed prior to renal failure show the same distribution of employment as the patient population as a whole. We have shown that those patients with more education are more likely to be employed prior to dialysis, as well as on dialysis, and nearly 70% of those patients who were employed prior to dialysis are working after transplant. The numbers are reduced as the amount of education decreases.

The rehabilitation of patients, as far as activity is concerned is more successful than employment. These patients feel better after transplant, and can lead more normal lives than while on dialysis. Only 19% of the patients felt they could lead a normal life while on dialysis, while 53% thought the same after transplant.

Sexual function was also better after transplant, than while on dialysis, although a significant number of patients had no sexual function at all during this time.

Our results indicate that the long-term effects of transplantation were favorable. Even though the number of patients entering the work field has not changed in contrast to other studies, these patients can contribute in other ways, as well as lead more normal lives.⁵ It is possible that our results do not reflect what other groups have found,³⁻⁵ because our patient population tended to be less educated and had other associated problems such as drug addiction and socioeconomic difficulties which may lead to the less favorable results of rehabilitation after transplant.

In summary, our experience indicates that the employment rehabilitation of transplant patients was not significantly better than in dialysis. The level of activity was better after transplant than dialysis. Transplantation, in general, made the patients feel better, have less medical problems and were physically more active than when they were on dialysis.

Resumen: La rehabilitación después del transplante en pacientes con enfermedad renal terminal es estudiada en 106 sujetos que recibieron 117 transplantes. Cincuenta y tres porciento de nuestros pacientes estaban empleados antes del transplante. Después del transplante, no existió ningún aumento en el empleo de los pacientes. En general, los pacientes que recibieron transplantes, se sintieron mejor y estuvieron fisicamente más activos que los pacientes en diálisis. Unicamente 19% de los pacientes en diálisis se sintieron que llevaban una vida normal, cuando 40% tuvieron la misma sensación después del transplante. A pesar de la mejoría obtenida después del transplante, todavía 31% los pacientes no fueron sexualmente funcionales.

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What can you do for hypertensives like these?



Rely on one-tablet-a-day for these and virtually

Laura K is depressed... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN® (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits ... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Smoking has been implicated-especially in males. Cardioselective **TENORMIN** exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence. Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³ At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen. Unlike propranolol, cardioselective TENORMIN can reduce the likelihood of bronchospasm in

susceptible

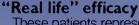
patients.5



dosage and cardioselectivity all your hypertensives.

Newly diagnosed ... workup shows 162/100 mmHq. On cimetidine for peptic ulcer. Don S hates the thought of yet another medication.

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when it is administered concomitantly with cimetidine 7,8 or ranitidine.9



These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.3

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.3

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.3

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.10



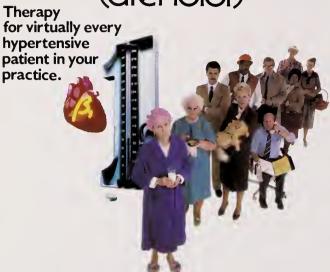
*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.



See following page for brief summary of prescribing information.







TENORMIN® (atenolol) A beta,-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN* (atenoiol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2²-hydroxy-3²-[41-methylethyl) amino] propoxy]. Atenoiol (free base) has a molecular weight of 266 lt is a relatively polar hydrophilic compound with a water solubility ol 26 5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C) and less soluble in 1N HCl (300 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenoiol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiszide-type diuretic.

thiazide-type diuretic

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater
than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory
function in congestive heart failure, and beta blockade carries the potential hazard of further
depressing myocardial contractifity and precipitating more severe failure in hypertensive patients
who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be
administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with
beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first
sign or symptom of impending cardiac failure, natignts should be fully diquitatived and for be onlyed a

beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and / or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta,-stimulating agent (bronchodiliator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic

the last dose and anesthesia if freatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (e.g. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V.)

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosls: Beta-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely
PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).
Drug Interactions: Catecholarime-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholarime depletor should therefore be closely observed for evidence of hypotension and/or marked brady-cardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

of clonidine Carcinogenesis, Mutagenesis, Impairment of Fertillity: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vaculation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose.

respectively)
USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo / fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12 5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

atencial Pediatric Use: Safety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg. by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain

these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain. The following adverse-reaction data present frequency estimates in terms of percentages first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects).

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), triedness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), dreaming (0%-0.9%)
GASTROINTESTINAL diarrined (2%-0.9%), nausea (4%-1%), RESPIRATORY (See WARNINGS), wheeziness (0%-0.9%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrined (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS There have been reports of skin rashes and / or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenoloi)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional liability with slightly clouded sensorium, decreased performance on neuropsychometrics

Gastrointestinal: Mesenteric arienal thrombosis, ischemic colitis

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomicocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

reaction

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Aminophylline, isoproterenol, or atropine.

epinephrine may be useful in addition to atropine and digitalis.

Bronchospasin: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type duretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1 73 m²)	Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day
Dationto on homodialusio ob	auld be awar EO ma affor each dialus	is: this should be done under

Patients on hemodialysis should be given 50 mg affer each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur HOW SUPPLIED: Tables of 50 mg TENORMIN (altenolo); round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (altenolo); round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Sciatica y Quimionucleolisis

Joseph E. Ortíz, M.D., FAAOS Joseph E. Rojas, M.D., FAAOS

Resumen: En casos de sciatica debido a un disco herniado lumbar, la quimionucleólisis nos provee con un método de tratamiento eficaz y seguro en aquellos casos en los cuales ha fallado el tratamiento conservador. Mediante una selección meticulosa y una técnica quirúrgica precisa los resultados a obtener serán magníficos.

Este estudio consta de setenta y siete pacientes con disco herniado lumbar que fueron tratados con quimopapaína intradiscal. Todos eran candidatos para tratamiento con cirugía abierta. Ochenta y ocho porciento de los pacientes obtuvieron resultados excelentes o buenos sin ninguna complicación. Aunque aparenta sencillo, este tratamiento requiere atención al detalle de diagnóstico y técnica quirúrgica.

a sciatica es un síntoma que puede estar presente en varias entidades clínicas. Una de ellas es la herniación de un disco lumbar. Dicha entidad usualmente se presenta inicialmente como dolor en la parte baja de la espalda. Solamente el resfriado supera al dolor de espalda como la razón primordial por la cual se visita al médico en el mundo entero. El impacto económico del dolor de espalda se considera sea alrededor de \$25 billones en los Estados Unidos solamente.

Anterior al 1982 el único método de tratamiento disponible para la herniación discal, una vez el manejo conservador no había sido eficaz, era la laminectomía y extirpación del nucleo pulposo. Para ese tiempo cerca de 200,000 procedimientos quirúrgicos se estaban llevando a cabo anualmente en los Estados Unidos con resultados mixtos. En noviembre de 1982 la Administración de Drogas y Alimentos de los Estados Unidos luego de un estudio controlado, aprobó el uso de la quimopapaína en el tratamiento de discos herniados. Este estudio presenta nuestra experiencia con sesenta y siete pacientes puertorriqueños que viajaron a Titusville, Florida con el propósito de someterse a la quimionucleólisis.

Apuntes Históricos

La papaína, un extracto de la savia de la papaya, contiene varias enzimas proteolíticas. Quimopapaína es una de ellas. Thomas fue el primero en describir los efectos de la papaína en cartílago. Luego Hirsch en 1959, consideró la posibilidad de aliviar los síntomas de un disco herniado mediante la inyección de una enzima proteolítica en el núcleo pulposo. Cinco años más tarde, luego de varios estudios e investigaciones en el laboratorio, Smith publica sus experiencias con el uso clínico de

quimopapaína. Le siguen a estos una multitud de investigaciones, unas a favor y otras en contra, culminando finalmente en la aprobación de la droga en noviembre de 1982.

Selección de Pacientes

Solamente aquellos pacientes con disco herniado lumbar fueron seleccionados. Para establecer ese diagnóstico era necesario satisfacer los siguientes requisitos.

- 1. Dolor en la pierna de tipo radicular, como síntoma principal.
- 2. Parestesias o adormecimiento en patrón radicular.
- 3. Signo de Lassegue positivo.
- 4. Dos de los siguientes hallazgos deben estar presente: disminución de reflejos, debilidad muscular, disminución de sensibilidad.
- 5. Confirmación de los hallazgos clínicos por tomografía computarizada o un mielograma.

Materiales y Métodos

Setenta y siete pacientes puertorriqueños se sometieron a la quimionucleólisis desde julio de 1983 hasta noviembre de 1984. Treinta y siete de ellos varones y cuarenta hembras. Sus edades fluctuaban entre los diez y ocho años y los sesenta y ocho con un promedio de cuarenta y dos años de edad. Cada uno de los pacientes fue diagnosticado utilizando las cinco pautas mencionadas anteriormente. Ningún paciente tenía historial previo de cirugía en la columna vertebral.

Veintisiete pacientes fueron inyectados en el nivel L5/S1, cuarenta y uno en el nivel L4/5, uno en el nivel L3/4, cinco en los niveles L4/5/S1, y tres en los niveles L3/4/5. El tiempo en el cual los síntomas se hallaban presentes fluctuó entre seis semanas y nueve años con un promedio de veintidos meses. El período de seguimiento fue desde un mínimo de tres meses hasta veinte meses. Todos los procedimientos fueron llevados a cabo estando ambos autores presentes.

Procedimiento Quirúrgico

La droga utilizada fue chymopapain (Chymodiactin), preparada por los laboratorios Smith. Con el propósito de minimizar el riesgo de anafilaxis, se administraban las siguientes drogas 24 horas antes del procedimiento: Cimetidine 300 mgm p.o. q 6h, Diphenhydramine 50 mgm p.o. q 6h. Una vez anestesiado el paciente, se colocaba en posición decubito lateral izquierda. Mediante el uso del abordaje lateral-posterior y bajo fluoroscopía, se introducía una aguja número 18 dentro de el nivel correspondiente. La posición de la aguja era verificada no solo con el intensificador de imágenes sino también con placas permanentes. Luego se inyectaba 0.3cc de la

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droga. Si al cabo de quince minutos no había ocurrido ninguna reacción alérgica entonces se procedía a inyectar el resto de la quimopapaína lentamente. De ahí el paciente se pasaba a la sala de recuperación, en la cual era observado cuidadosamente por una hora antes de retornar a su habitación.

Manejo Post-Inyección

A los pacientes se les permitía estar fuera de la cama en cuanto regresaban a su habitación. Durante las siguientes tres semanas se aumentaban sus actividades lentamente y al final de ese período se le permitía llevar a cabo trabajo de oficina solamente. Al cabo de seis semanas ya los pacientes en su immensa mayoría, se hallaban listos para comenzar un programa de terapia física y rehabilitación.

Evaluación y Clasificación

Todos los pacientes fueron examinados durante varias ocasiones por ambos autores y fueron evaluados usando los siguientes criterios:

EXCELENTE: Ausencia de síntoma alguno, ausencia de hallazgos físicos y capaz de llevar a cabo cualquier actividad de trabajo o recreativa. BUENO: Dolor de espalda residual que necesita analgésicos como acetaminophen y relajantes musculares ocasionalmente. Ninguna restricción en sus actividades.

LEVE MEJORIA: Todavía requieren narcóticos tipo III o IV para el alivio de sus síntomas. Restringidos moderamente en su trabajo pero no en sus actividades del diario vivir.

NO MEJORIA: Síntomas y hallazgos no han cambiando en absoluto.

Resultados

Cincuenta y ocho pacientes (75%) obtuvieron resultados excelentes, diez (13%) obtuvieron resultados buenos, cuatro (5%) tuvieron leve mejoría y cinco (6%) no tuvieron mejoría alguna. Veintiseis (35%) desarrollaron espasmos musculares severos durante el período post operatorio inmediato. Ningún paciente ha sufrido recidiva alguna.

NIVEL L5/S1

Un total de veintisiete pacientes fueron inyectados a este nivel. Veintiuno tuvieron resultados excelentes, dos tuvieron resultados buenos, uno obtuvo leve mejoría y tres no obtuvieron mejoría alguna.

NIVEL L4/5

Cuarenta y un pacientes fueron inyectados a este nivel. Treinta y dos obtuvieron resultados excelentes, cinco obtuvieron resultados buenos, dos obtuvieron leve mejoría y dos no obtuvieron mejoría alguna.

NIVELES MULTIPLES

Ocho pacientes fueron inyectados en dos niveles. Cinco obtuvieron excelentes resultados y tres obtuvieron buenos resultados.

COMPLICACIONES

Ningún paciente sufrió reacción alérgica alguna ni ningún problema de índole neurológico, inmediato o tardío. No hubo infecciones. El único problema si se puede llamar problema fueron los espasmos paravertebrales severos, que ocurrieron en el 35% de los casos. Usualmente esto nos obligaba a alargar la estadía del paciente en el hospital un promedio de un día adicional.

FRACASOS

Se consideraba un fracaso el tratamiento, cuando después de pasados noventa días no se había detectado mejoría alguna en el paciente. Cinco pacientes se tuvieron que incluir en esta clasificación. En dos de estos pacientes el nivel inyectado estaba relativamente degenerado antes de hacerse el procedimiento y aparentemente no había suficiente núcleo pulposo para disolver. Uno de estos pacientes fue operado y el cirujano reportó el hallazgo de estenosis vertebral. De los otros tres pacientes, uno tenía espuelas oseas en niveles distintos al inyectado, en otro se sospecha tenga un fragmento de disco suelto en el canal espinal y en el tercero no se encuentra razón alguna. Ninguno de los pacientes con leve mejoría se han operado.

DISCUSION

Nuestro estudio demuestra que en casos de disco herniado lumbar que no han respondido a tratamiento conservador, la quimionucleólisis con quimopapaína es un tratamiento eficaz y seguro. Es de vital importancia el escoger los pacientes muy cuidadosamente. Para nuestro estudio, unicamente aquellos pacientes que satisfacían nuestras cinco pautas diagnósticas fueron seleccionados. Creemos pués, que de seguir estas pautas fielmente, resultados similares se podrían obtener en cualquier lugar.

Recientemente se han reportado complicaciones neurológicas severas tales como la mielitis transversa luego de quimionucleólisis. Se sabe que si la quimopapaína se inyecta dentro del saco espinal ocurre una reacción tóxica severa acompañada por hemorragia subaracnoidea. De mezclarse la quimopapaína con un tinte radio-opaco la reacción es aún más tóxica. A raíz de esos reportes se eliminó la discografía como parte del procedimiento y además se hizo hincapié en que el procedimiento se debería llevar a cabo por un cirujano experimentado en quimionucleólisis para asi evitar cualquier posibilidad de penetrar el saco espinal con la aguja de quimonucleólisis. Luego de sentarse estas pautas, no se han reportado más casos de mielitis transversa luego de quimionucleólisis. Creemos que no solamente el eliminar la discografía sino el hacer énfasis en el procedimiento es lo que ha eliminado esta terrible complicación. Hemos desarrollado un método sencillo, el cual toma en consideración las distintas tallas de los pacientes y nos permite guiar la aguja de quimionucleólisis sin ningún problema hacia el sitio indicado. Nuestro método será publicado en un futuro cercano.

Luego de analizar los fracasos encontramos que aunque dichos pacientes satisfacían nuestros criterios de diagnóstico, algunos de ellos presentaban ciertas anormalidades anatómicas que a nuestro entendimiento jugaron un papel importante en evitar un buen resultado. Creemos que de detectarse las siguientes condiciones junto a un disco herniado se debería considerar el no usar quimopapaína. Dichas condiciones son: inestabilidad de la columna vertebral, degeneración discal moderada o severa y estrechez del foramen intervertebral. Para poder descartar lo arriba mencionado es de suma importancia el obtener una tomografía computarizada de la mejor resolución y calidad. De esa manera solamente aquellos casos con sciatica debido a un disco herniado serán seleccionados para el tratamiento con quimopapaína.

No podemos de dejar de mencionar el impacto económico de la quimionucleólisis. El costo es alrededor de 50% del costo usual del tratamiento quirúrgico (laminectomía).

Summary: Chemonucleolysis provides us with a safe and effective therapeutic method for the patient with a herniated lumbar disc who has not responded to conservative management. With proper patient selection and precise surgical technique the results to be obtained can equal or surpass those of laminectomy.

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SOCIOS NUEVOS



ACTIVOS

Beauchamp Feliciano, Pedro J. MD - Universidad de Puerto Rico, 1976, Obstetricia y Ginecología. Ejerce en Bayamón.

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Núñez de la Cruz, Lorenzo C., MD - Universidad Autónoma de Santo Domingo, República Dominicana, 1963, Anestesiología. Ejerce en Río Piedras.

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Rosado Rosado, Rosaura, MD - Universidad Central del Este, San Pedro de Macorís, República Dominicana, 1978, Medicina General. Ejerce en Vega Baja.

AFILIADO

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REINGRESO

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Presentación de Casos

Acute Colonic Pseudo-Obstruction (Ogilvie's Syndrome): A Case Report Showing the Benefit of Colonoscopy

Evelio F. Bravo-Fernández, M.D. Esther A. Torres, M.D. Juan Zaiter, M.D.

Abstract: Acute colonic pseudo-obstruction was described by Ogilvie in 1948 as a massive dilatation of the colon without obstruction in the large bowel. Its clinical and radiological manifestations resemble a mechanical obstruction. In view of the risk of cecal perforation, decompressive cecostomy has been recommended in the past. Recently, colonoscopy has been reported as an effective diagnostic and therapeutic tool in this condition. We present a case of acute colonic pseudo-obstruction revealing the benefit of colonoscopy in the diagnosis and treatment of this condition.

A cute colonic pseudo-obstruction was first described by Ogilvie in 1948 as an acute massive dilatation of the large bowel without an organic obstruction. In 1980, Nanni et al summarized the reported cases and found that 88% of them were associated with various extracolonic conditions such as metabolic disturbances, severe cardiac or pulmonary diseases, postoperative periods and trauma.²

The clinical and radiological manifestations of this syndrome resemble a mechanical obstruction of the colon with dilatation of the cecum or the entire colon. The massive cecal dilatation can compromise the mucosal circulation and lead to perforation with a mortality rate of 46%.³ For this reason, decompressive tube cecostomy has been recommended in the past. Nevertheless this procedure, when used in cases of acute colonic pseudo-obstruction, has been associated with a mortality rate of 20%.⁴

In 1977 Kukora and Dent⁵ reported the successful colonoscopic decompression in five patients with massive acute colonic pseudo-obstruction. Recently colonoscopy has been shown to be a reliable, effective and safe procedure in the diagnosis and treatment of this condition.⁶⁻⁹

The purpose of this presentation is to call to the

attention of our colleagues the general features of this syndrome with particular emphasis on colonoscopy as a new diagnostic and therapeutic alternative.

Case Report

A 55-year-old man with history of heavy alcohol intake was brought to our Emergency Room after an episode of dizziness, loss of consciousness and loss of urinary continence. After awakening, the patient was somewhat confused and complained of headache. There was no history of head trauma.

Upon physical examination, the temperature was 37.5° C, the blood pressure 190/110, pulse was 64 beats per minute. The rest of the physical exam was unremarkable except for a decrease in motor strength on the left side and a left Babinski. All the basic laboratories were within normal limits except for a moderate leukocytosis. A CT-scan revealed an intracerebral hemorrhage draining into the ventricular system.

The patient was admitted to the Neurosurgery service and was treated medically with adequate response. Four days later, his abdomen became distended. A KUB revealed dilatation of the large bowel (Fig. 1), and our gastroenterology service was consulted. At this time the patient denied recent changes in bowel habits, significant weight loss, hematochezia, pencil like stools, abdominal pain, or fever. The abdominal distention was obvious at inspection, with marked tympanism to percussion, but adequate peristalsis. There were no peristaltic rushes and no tenderness nor rebound tenderness were elicited upon palpation. Rectal exam and guaiac were negative. The laboratories were within normal limits except for the leukocytosis and a serum potassium level of 3.1 mEq/L (NV 3.5-5.0). The possibility of Ogilvie's syndrome was considered in the differential diagnosis. Because the cecum meassured 9 cms in diameter and it is well known that there is a real risk of cecal perforation in this circumstance, 10 a diagnostic and therapeutic colonoscopy was done. The bowel was prepared with one enema (one liter of tap water), not with the intention of cleansing the colon but to liquefy the stools. One hour later, the

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Olympus (CFLB3W) colonoscope was inserted and advanced without air insufflation up to the ascending colon. A large quantity of liquid stool and air was suctioned, with resolution of the abdominal distention. After colonoscopy his cecal diameter was 3 cms (Fig. 2). Since no obstructive lesion was identified, the diag-



Figure 1. Acute colonic pseudo-obstruction. Plain film of the abdomen revealing the colonic dilatation in our case.



Figure 2. Acute pseudo-obstruction during colonoscopy. Plain film of the abdomen showing the colonoscope with an "alpha loop" inserted into the cecum. Note the significant decrease in cecal distention. Further reduction in the diameter of the colon was obtained by suction of air and water as the scope was withdrawn.

nosis of Ogilvie's syndrome was corroborated. In the next three days, the patient had gradual reaccumulation of air in the colon that resolved with intermittent nasogastric suction, correction of serum potassium deficit, treatment of a urinary tract infection and of his neurologic condition. The patient's condition improved, regaining normal bowel function approximately seven days after the acute colonic dilatation developed. Finally, he was discharged with a minimal residual left hemiparesis.

Discussion

Acute colonic pseudo-obstruction has been described with such terms a nontoxic megacolon, Ogilvie's syndrome, adynamic ileus of the colon, false colonic obstruction, pseudomegacolon, hypokalemic illeus of the colon and nonobstructive colonic dilatation, 7-9 but should not be confused with chronic intestinal pseudo-obstruction. The latter, is a chronic illness characterized by symptoms of recurrent intestinal obstructions without demonstrable mechanical occlusion of the bowel. In addition, these patients present achalasia of the esophagus. Most patients have their first episode early in life and the principal symptoms are crampy abdominal pain, vomiting, distention, diarrhea and steatorrhea in some cases.¹¹

Ogilvie¹ theorized that interruption of the sympathetic supply to the large intestine, leaving the parasympathetic invervation unopposed was the more probable explanation. More recently, other authors have postulated an imbalance of the autonomic inervation of the colon;² but sacral parasympathetic denervation has been suggested as the more probable cause to the clinical picture of pseudo-obstruction by others. ¹²⁻¹³ At present, the etiology of this colonic distention is not completely clear. Nevertheless, because of the associated conditions in our patient (intracerebral hemorrhage, hypokalemia, alcoholism and urinary tract infection) the possibility of an autonomic imbalance seems a likely explanation.

The treatment of this condition should include placing the patient NPO, intermittent nasogastric suction, electrolyte and fluid replacement plus agressive treatment of associated conditions. Serial abdominal plain films are of paramount importance because this condition can progress rapidly and lead to spontaneous cecal perforation in about 14% of the cases.² Once perforation has occurred the mortality rate increases to 46%.3 For this reason, if the previously outlined management fails to control the cecal distention, emergency surgery is indicated to decompress the colon. Surgery is usually poorly tolerated by these patients due to the associated medical conditions. For example, decompressive cecostomy has been considered a simple and easy procedure with low morbidity,14-15 yet in patients with Ogilvie's syndrome, it has been associated with a high morbidity.4 Recently, decompressive colonoscopy has been performed with a success rate of 86-100% without direct complication from the procedure. 6-9

Our case demonstrates the effectiveness of colonoscopic decompression, which has the advantage of ruling out colonic obstruction as well as directly treating the cecal

dilatation. However, colonoscopy should be performed with minimal air insufflation. In a poorly prepared colon, this procedure is technically demanding and time consuming. We used small amounts of water injected through the water-air channel of the colonoscope as needed to make possible the visualization of the lumen. Our observation in this case was that air insufflation was not as important as it is in a routine colonoscopy, probably because of the already pathologically distended colon.

We believe that colonoscopy is a valuable alternative of cecal decompression in patients with acute pseudo-obstruction. However, the potential hazard of the procedure must be recognized and the endoscopist must introduce the scope very cautiously. If there is any evidence of ischemia of the colon (bloody drainage, purple or friable hemorrhagic mucosa), the procedure should be immediately terminated and laparotomy carried out.

Resumen: La pseudoobstrucción colónica aguda fue descrita por Ogilvie en el 1948 como una dilatación masiva del colon sin una obstrucción en el intestino grueso. Sus manifestaciones clínicas y radiológicas semejan una obstrucción mecánica. Debido al riesgo de perforación del ciego, se ha recomendado en el pasado la cecostomía decompresiva. Recientemente, se ha reportado el uso eficaz de la colonoscopía como método diagnóstico y terapéutico en esta condición. Presentamos un caso de pseudoobstrucción aguda de colon, que ejemplifica el beneficio de la colonoscopía en el diagnóstico y tratamiento de esta condición.

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REVIEW ARTICLES

Persistent Pulmonary Hypertension of the Newborn: Diagnosis and Management by the Primary Care Physician

Gloria Reyes Baez, M.D. Carlos A. Pérez, M.D.

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome described more than ten vears ago. It represents a group of newborn infants that present with cyanosis due to pulmonary hypertension with shunting of blood through the ductus arteriosus and/or the foramen ovale. A high pulmonary vascular resistance is normally present during fetal life. This high vascular resistance is a consequence of the low oxygen tension of the fetal blood. After birth a reduction in the pulmonary resistance is necessary for survival. In certain occasions this reduction in the pulmonary vascular resistance does not occur. Some of the factors that prevent this normal reduction of the pulmonary vascular resistance are hypoxia, hypercarbia, hypoglycemia, hypothermia and the presence of vasoactive substances. Hypoxia is the most potent inducer of pulmonary vasoconstriction.

Babies who develop PPHN are usually term and postterm infants. Most of these babies have been exposed to hypoxia during pregnancy and/or delivery. Infants of diabetic mothers and infants born by elective cesarean sections are also at higher risk of developing pulmonary hypertension. Babies with perinatal asphyxia, intrauterine pneumonias, meconium aspiration, respiratory distress syndrome and transient tachypnea of the newborn are also at risk of developing the syndrome of PPHN. A careful diagnostic workup should include a chest x-ray, determination of the hematocrit, serum glucose and a careful analysis of the arterial blood gases. In many cases the diagnosis of congenital heart disease cannot be excluded. The management of the patient with cyanosis includes correction of metabolic abnormalities and avoidance of hypoxia. Once the diagnosis of PPHN is done, inmediate transfer to a tertiary care center is necessary.

In 1969, Gersony and associates¹ described two newborn infants who presented with cyanosis in the absence of pulmonary disease, central nervous system disturbance or cardiac disease. At cardiac catheterization, these babies had pulmonary hypertension and right to left shunting of blood through the ductus arteriosus and the foramen ovale. Due to the similarity of this condition to the circulation of the fetus in utero, he called it persistence of the fetal circulation (PFC).

In 1976, Levin and collaborators² used the more descriptive term of persistent pulmonary hypertension of the newborn (PPHN) to describe eleven babies that presented with cyanosis due to pulmonary hypertension. Right to left shunting of blood through the ductus arteriosus was documented in nine of these babies.

During the past ten years, a better understanding of the syndrome of PPHN has been gained. The presence of pulmonary hypertension with right to left shunting of blood at the atria and/or the ductus arteriosus has been recognized in a variety of neonatal pulmonary diseases. Among these are intrauterine pneumonias,³ meconium aspiration syndromes,⁴ hyaline membrane disease⁵ and hypoplastic lungs.³ Early recognition of babies at risk of developing PPHN is possible. Despite mayor advances in management, the treatment of babies with PPHN continues to be difficult and complicated; therefore, it should be reserved to a tertiary care center.

In this article, we will review this clinical condition (best described as persistent pulmonary hypertension of the newborn), for the primary care physician. Special emphasis will be placed in early diagnosis and management.

Pathophysiology

The circulatory pattern of the fetus consists of a low pressure systemic circuit and a high pressure pulmonary circuit. The placenta is in the low pressure circuit serving as the organ of respiration. The high pressure circuit consists of the pulmonary circulation with its characteristically high vascular resistance. The oxygenated blood

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coming from the placenta enters the right atrium through the inferior vena cava. From the right atrium about 75% of the blood will be directed to the left side of the heart through the foramen ovale. This blood, which is adequately oxygenated for the fetus, will perfuse the heart and the brain, which are the organs with the highest oxygen demands. The blood that returns from the head through the superior vena cava, mixes with the blood that was not shunted to the left atrium and drains into the right ventricle. From the right ventricle, the blood passes into the pulmonary artery, from where 85-90% will pass through the ductus arteriosus into the lower pressure descending aorta. The lungs, which at this time of life serve no respiratory function, receive only 8% of the cardiac output. 6, 7, 8 (Figure 1)

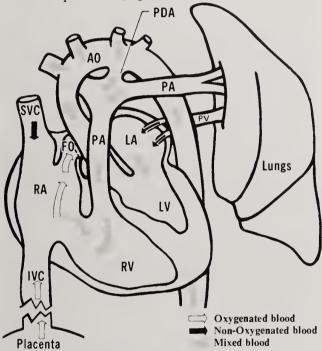


Figure 1. Diagrammatic representation of the fetal circulation

IVC: Inferior vena cava, RA: Right atrium, SVC: Superior vena cava, FO: Foramen ovale, LA: Left atrium, LV: Left ventricle, PA: Pulmonary artery, AO: Aorta, RA: Right ventricle, PV: Pulmonary vein, PDA: Patent ductus arteriosus.

One of the main determinants of the fetal circulation is the high pulmonary vascular resistance, which is due to the anatomic characteristics of the pulmonary arterioles and their response to various stimuli. The pulmonary arterioles have a thick muscular layer which contracts in the presence of low oxygen tensions.9, 10 During intrauterine life, the PO₂ in the pulmonary artery is 18-21mmHg. This maintains the pulmonary arteries in a state of vasoconstriction. As gestation advances, the thickness of the muscular layer of the pulmonary arterioles increases, and as the pulmonary arterioles acquire more muscle, their response to hypoxic stimuli increases. Chronic intrauterine hypoxia will produce hypertrophy of this muscular layer.9, 10, 11 As a consequence of these changes in the pulmonary arterioles a reduction in the internal diameter of the vessel occurs. This in turn produces an increase in the resistance of flow through the pulmonary artery.8, 9

After birth, a rearrangement of the circulation is necessary for survival of the newborn infant. The placenta is eliminated from the circulatory circuit and the lungs take over the function of respiration. All the blood must go to the lungs for oxygenation. In order for these changes to occur, the pulmonary vascular resistance must decrease and must be lower than the systemic circulation. Two situations occur to facilitate the decrease in pulmonary resistance. First, the increase in alveolar PO₂ that occurs after birth induces relaxation of the muscular layer of the pulmonary arterioles. This will inmediately produces a decrease in the pulmonary vascular resistance and an increase in the flow of blood through the lungs. Second, a rapid decrease in the amount of muscle in the pulmonary arterioles occurs a few hours after birth. This will produce a further decrease in the pulmonary vascular resistance.7, 8, 10, 12 (Figure 2)

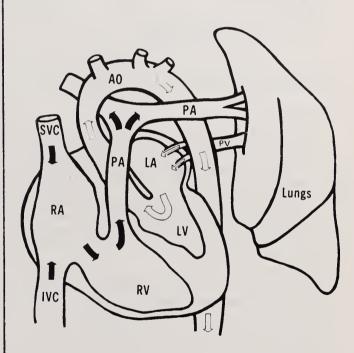


Figure 2. Diagrammatic representation of the normal post-natal circulation

Failure to achieve an adequate oxygenation in the newborn infant, causes pulmonary vasoconstriction to persist or to recurr; thus causing, an increase in the pulmonary vascular resistance.^{5, 10} Since the foramen ovale and the ductus arteriosus remain potentially open during the first few days of life, an increase in the pulmonary vascular resistance will cause shunting of blood through the ductus arteriosus and/or the foramen ovale. As a consequence, the infant will become hypoxic and a further increase in the pulmonary vascular resistance will occur. (Figure 3)

Many factors are known that produce pulmonary vasoconstriction. Some of these factors are hypoxia, ¹⁰, ¹² acidosis, ¹⁰, ¹³ hypercarbia, ¹⁴ bacterial toxins, ¹⁵, ¹⁶ hypothermia, ¹⁷ polycythemia, ¹⁸, ¹⁹ and many vasoactive substances. ²⁰, ²¹ Of these, hypoxia is the most potent cause of pulmonary vasoconstriction.

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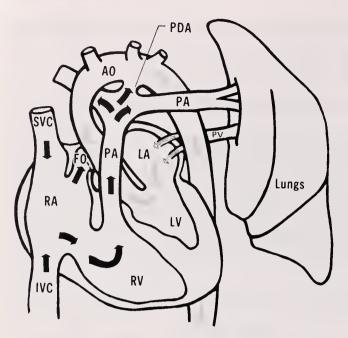


Figure 3. Diagrammatic representation of the blood circulation in persistent pulmonary hypertension of the neonate (PPHN)

Patient Profile

Persistent pulmonary hypertension of the newborn is a disease of the term and post-term infant.^{2, 3, 5} Complications during pregnancy and delivery, predisposing to fetal hypoxia, are common in infants with PPHN. Preeclampsia, hypertension, advanced maternal age, drug addiction and prolonged gestations are the most common complications. During delivery, the presence of meconium in the amniotic fluid and low Apgar scores are important risk factors.^{2, 3}

Premature and term infants with the respiratory distress syndrome can develop PPHN.^{5, 22} A higher incidence of the respiratory distress syndrome is seen in infants of diabetic mothers. This is attributed to a delayed maturation of the synthesis of surfactant.^{23, 24} Elective C-sections are also associated with an increased incidence of respiratory distress syndrome. Assessment of the fetal lung maturation prior to elective C-sections is necessary to avoid this complication.^{26, 27, 28}

Infants of diabetic mothers, who have not had strict control of their diabetes during pregnancy, have been found to have a higher incidence of pulmonary hypertension.^{24, 25}

Babies with intrauterine pneumonias and with meconium aspiration syndromes are at high risk of developing pulmonary hypertension. These babies are usually those who have been exposed to asphyxia. Certain bacterial toxins cause pulmonary vasoconstriction.¹⁵, ¹⁶, the classical example is infection with group B-streptococcus.¹⁵ Babies with radiologic diagnosis of transient tachypnea of the newborn may present with PPHN. These infants present with hypoxemia early in the course of their disease.²⁹

The baby with PPHN presents with respiratory symptoms since birth or shortly after. The need for increasing oxygen concentration is characteristic of these newborn infants. ²⁰, ³⁰⁻³² Some may present with a sudden

onset of cyanosis and shock during the first 24 hours of life. This presentation is more common in the presence of infection.³²

Diagnosis

A basic work-up is necessary to diagnose the cause of cyanosis in the newborn. A chest x-ray is important to diagnose causes of cyanosis such as diaphragmatic hernia, pneumothorax, pneumonia, respiratory distress syndrome or intrathoracic masses. A hematrocrit must be done to rule out polycythemia as the cause of the cyanosis.¹⁸ Polycythemia is a common and easily treated cause of pulmonary hypertension. An increase in the hematocrit produces an increase in the viscosity of the blood, and as a consequence, there is an increase in the pulmonary vascular resistance. 19 This occurs when the central hematocrit is above 65vol.%. A partial exchange transfusion with normal saline or plasma will lower the blood viscosity and produce a decrease in the pulmonary vascular resistance. Hypoglycemia is another cause of cyanosis in the newborn period. It produces an increase in the pulmonary vascular resistance with right to left shunting of the blood through the ductus arteriosus.¹⁹

Analysis of the arterial blood gases in high oxygen concentrations will help in determining the etiology of the cyanosis.², ³, ³⁰ A PaO₂ of less than 50mmHg in 100% oxygen is suggestive of severe persistent pulmonary hypertension versus congenital heart disease. The presence of a heart murmur favors the diagnosis of heart disease, although, patients with PPHN may present with heart murmurs. A newborn infant with cyanosis and a heart murmur requires an inmediate evaluation by a pediatric cardiologist. Babies with PaO, of more than 50mmHg but less than 100mmHg in 100% oxygen concentration, are more likely to have PPHN. The demonstration of a differential in oxygen tension between the preductal (higher PaO₂) and postductal (lower PaO₂) blood of over 15mmHg will indicate the presence of shunting of blood through the ductus arteriosus. This can be ascertained by obtaining a sample of blood from the right radial artery (preductal) and comparing its PaO₂ with that from the left radial artery or the abdominal aorta (postductal). A differential in oxygenation can be demonstrated in 50% of the cases with PPHN, the latter is more common early in the course of the disease. If the infant has severe pulmonary hypertension, the shunting of blood occurs both through the ductus arteriosus and foramen ovale. In this case no differential in oxygenation will be demonstrated between the preductal and postductal blood.

Management

Once the diagnosis of PPHN is suspected, arrangements should be done for immediate transfer of the patient to a tertiary care center. Sufficient oxygen should be administered to alleviate the cyanosis. In the cyanotic patient, the oxygen concentration should be maintained at 100% and no attempts should be done to decrease it. Although there is no evidence that this is correct, the general consensus is that these babies do better when the

oxygen concentration is maintained stable during the critical part of the disease.^{3, 31, 33} Special care should be taken to avoid sudden decreases in the oxygen concentration at all times. Babies with PPHN respond with catastrophic falls in PaO₂ to small decreases in the oxygen concentration.^{31, 33} They usually require high oxygen concentrations during the first 48-72 hours of life.^{3, 31, 33} During transfer and during the first few days of life, babies with PPHN should be maintained in 100% oxygen concentration. The use of 100% oxygen during the first few days of life has not been found to be associated with the development of pulmonary oxygen toxicity.³³

Supportive management should include the maintainance of an adequate blood pressure, acid-base balance and temperature. Hypotension due to perinatal blood loss should be corrected with blood or volume expanders. If the arterial pH is less than 7.25, sodium bicarbonate (7.5%) may be given at a dosage of lcc/kg diluted in an equal amount of sterile water. The vasoconstrictor effect of hypoxia is enhanced in the presence of acidosis. 13 If the pC0₂ is high, it is wiser to ventilate the baby first and then proceed to give the bicarbonate. Ventilation can be done with an Ambu bag. We do not recommend intubation of babies with PPHN unless an expert in intubating and ventilating newborns is available. The results of an unsuccesful prolonged intubation attempt is life threatening in babies with PPHT. Hypothermia induces increase of the pulmonary vascular resistance. 17 A skin surface temperature of 36-36.5°C should be maintained.

During transport, the baby should be maintained as comfortable as possible. An intravenous line should be secured and 10% dextrose in water, infused at a rate of 60cc/kg/day is recommended. Calcium gluconate (10%) may be added to the IV fluids at a dosage of 3cc/kg/day. A person with experience in neonatal resuscitation should accompany the baby during transport to the tertiary care center.

The mortality of babies with PPHN is high, despite mayor advances in therapy.^{3, 31} A mortality of around 40-50% is reported from most neonatal units. We hope that with early recognition and transfer to a tertiary care center we may improve the chance of survival of such neonates.

Conclusion

Persistent pulmonary hypertension of the newborn is a potentially lethal condition in the newborn period. Its prognosis will depend on the adequate identification and prevention of factors associated with pulmonary vasoconstriction during pregnancy and delivery (Table I). A careful prenatal care of the pregnant women is necessary in order to identify risk factors associated with fetal hypoxia so that a pediatrician, or other competent professional, be in attendance at the delivery of the newborn infant.

The primary care physician should have a fair knowledge of the situations associated with pulmonary vasoconstriction during the perinatal period (Table II), so that these may be avoided. Prompt and adequate resuscitation measures should be available for all high risk infants. If despite of all preventive measures the infant continues hypoxic, a careful evaluation is imperative for establishing the diagnosis of PPHN and determining the infant that requires transfer to a tertiary care center.

TABLE I

Factors Associated with Pulmonary Vasoconstriction

Hypoxia
Hypothermia
Acidosis
Hypercarbia
Hypoglycemia
Polycythemia
Bacterial toxins
Vasoactive substances

TABLE II

Complications Associated with PPHN

During pregnancy

Preeclampsia
Hypertension
Advanced maternal age
Drug addiction
Prolonged gestation
Diabetes mellitus

During delivery

Meconium in amniotic fluid Low apgar scores Elective cesarean sections

After birth

Meconium aspiration syndrome Intrauterine pneumonia Transient tachypnea of the newborn Perinatal asphyxia Respiratory distress syndrome Hyperviscosity syndrome

Resumen: El síndrome de hipertensión pulmonar persistente del recién nacido fue descrito hace más de diez años. Se presenta en recién nacidos con cianosis. Esta disminución del oxígeno sanguineo se produce como consequencia de un cortocircuito a nivel del ducto arterioso y/o el foramen oval, condición que esta determinada por un aumento en la presión pulmonar arterial.

Durante la vida intrauterina, la resistencia pulmonar es alta, después del nacimiento, ésta disminuye. En ciertas ocasiones esto no ocurre. Algunos factores que impiden esta reducción normal de la resistencia pulmonar son la hipoxia, la hipercarbia, la hipoglicemia, la hipotermia y la presencia de sustancias vasoactivas, siendo la hipoxia el más potente de los vasoconstrictores pulmonares.

Los neonatos que desarrollan el síndrome de hipertensión pulmonar persistente son usualmente infantes a término o post-término. La mayor parte han sufrido de hipoxia durante el parto y/o el nacimiento. Los infantes de madres diabéticas y los infantes nacidos por cesáreas electivas

también representan un grupo de alto riesgo para el desarrollo de hipertensión pulmonar persistente. Los infantes recién nacidos que han sufrido asfixia perinatal e infantes con pulmonía intrauterina, aspiración de meconio, el síndrome de angustia respiratoria y taquipnea transitoria del recién nacido representan otro grupo de alto riesgo.

Entre las pruebas de diagnóstico se debe incluir una radiografía de tórax, determinación del hematocrito y glucosa sanguínea y un análisis cuidadoso de los gases arteriales. En muchos casos el diagnóstico de enfermedad congénita cardíaca no puede ser excluído.

El manejo del paciente con cianosis incluye corrección de desórdenes metabólicos y el evitar la hipoxia. Una vez se hace el diagnóstico de hipertensión pulmonar persistente es necesario transferir el recién nacido de inmediato a un centro de cuidado terciario para su manejo.

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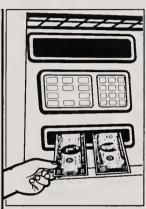
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Interaction of Third Generation Cephalosporins Combined With Amikacin Against Pseudomonas Aeruginosa

Julie R. Rodríguez, M.D. Nilda I. Hernández, M.D. Carlos H. Ramírez-Ronda, M.D. Minerva Nevárez, M.T.

Abstract: Cefoperazone, cefotaxime, moxalactam and ceftizoxime were tested alone and in combination with amikacin against 20 bacteremic strains of *Pseudomonas aeruginosa*. Utilizing the FIC index the most synergistic combination was ceftizoxime and amikacin (85%). If the data is analized by the effect of the antibiotic combination on the MIC for *Pseudomonas aeruginosa*, the most active *in vitro* combination was cefoperazone-amikacin. This apparent discrepancy may be confusing; we want to alert the clinician to be careful in utilizing *in vitro* synergy data as a therapeutic guide until clinical trials are performed and the *in vitro* findings are corroborated.

ombinations of antimicrobial agents are frequently necessary to provide broad spectrum coverage in patients who are seriously ill, particularly in leukopenic and immunosuppressed patients. Pseudomonas infections are frequent in this group of patients and traditionally an aminoglycoside plus an antipseudomonal Blactam antibiotic has been used to achieve additive or synergistic antibacterial activity and/or prevent emergence of resistance.⁴, ¹²⁻¹³

In the present study, the activity of four new third generation cephalosporins: cefoperazone, cefotaxime, ceftizoxime and moxalactam, alone and in combination with amikacin, was tested against 20 blood isolates of *Pseudomonas aeruginosa* from compromised hospitalized patients. The study was undertaken to define the *in vitro* synergistic activity of these newer agents combined with amikacin.

Twenty strains of *Pseudomonas aeruginosa* obtained from blood cultures of hospitalized compromised patients with serious infections from the Microobiology Laboratory of the Puerto Rico Medical Center and the San Juan Veterans Administration Hospital were studied. *Pseudomonas aeruginosa* ATCC 27853 (American Type Culture Collection, Rockville, Md.) was included as control. All strains were maintained lyophilized until tested. Synergy studies were performed at least in

duplicate in all isolates during a single 48-hour period.

Antibiotics. Sterile, standardized antibiotic powders were provided by their respective manufacturers: cefoperazone by Pfizer Pharmaceuticals (New York),

cefotaxime by Hoechst-Roussel Pharmaceutical (Somerville, New Jersey), moxalactam by Eli Lilly & Co. (Indianapolis, Indiana), ceftizoxime by Smith, Kline & French Laboratories (Philadelphia, Pa.), and amikacin by Bristol Laboratories (Syracuse, New York). Specific amounts of each antibiotic were diluted in their respective solvents to prepare stock solutions with a final

concentration of 1000 ug/ml.

Antibiotic combinations were prepared in microtiter plates served with the MIC 2000 96 Channel dispenser of the Dynatech Laboratories utilizing the checkerboard pattern as previously reported. The range of dilutions of the B-lactam agents was from 0.0625 to 64 ug/ml. Amikacin concentrations ranged from 0.25 to 16 ug/ml. On each plate one column of wells contained no B-lactam agent and one row of wells contained no amikacin. MICs of amikacin and the various B-lactam antibiotics for the 20 strains of Pseudomonas aeruginosa were read from these rows, respectively. One well per plate contained Muller-Hinton broth only to serve as a growth control. A plate with each antibiotic combination was not inoculated with organisms and served as a sterility control. All plates were kept frozen at - 80° C for a maximum of two weeks prior to use.

The MIC 2000 inoculator machine inoculated 0.0015 ml of standardized suspension of approximately $3x10^7$ CFU/ml (achieving a final inoculum concentration of approximately $4x10^5$ CFU/ml) to each well containing antibiotics. The trays were incubated at 35^9 C for 18 hours and examined for bacterial growth.

The MICs of the antibiotics tested, used alone or in combination, were defined as the lowest concentration of antibiotic that inhibited visible growth.

An antimicrobial combination was defined as synergistic if there was at least a fourfold decrease in the MIC of each antimicrobial agent; and was antagonistic if there was fourfold increase in the MIC of each one of the antibiotics in the combination. All other combinations were considered indifferent.¹²

Finally, another method of quantitating synergism, the fractional inhibitory concentration (FIC) index, was calculated as previously reported. For each row in the

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microtiter plate, the FIC index was calculated from the lowest concentrations of drugs necessary to inhibit growth. The FIC for each drug was derived by dividing the concentration of the drug present in that well by the MIC of the organism to that drug alone. The FIC index is then the sum of these values for both drugs at that point. When the FIC index is \leq .5, the combination is synergistic; when it is > 2.0, the combination is antagonistic. If the FIC index is > 0.5, and < 2.0, the combination is indifferent. If the sum is synergistic for some combinations of concentrations and antagonistic for others, the results are considered equivocal.

Example:

MIC for *P. aeruginosa* for amikacin = 16 ug/ml MIC of *P. aeruginosa* for ceftizoxime = 64 ug/ml

No growth occurred *in vitro* when amikacin-ceftizoxime were utilized at 4 and 16 ug/ml, respectively. Then, the FIC index for that combination is equal to the FIC of amikacin plus the FIC of ceftizoxime. That is:

$$FIC index = \frac{4}{16} + \frac{16}{64}$$

FCI index = .25 + .25

FCI index = 0.5 (synergism)

All 20 strains of *Pseudomonas aeruginosa* strains were susceptible to amikacin (MIC \leq 16 ug/ml). The first new third generation cephalosporins to have its breakpoint defined was cefotaxime.² Organisms are considered susceptible to cefotaxime or to other third generation cephalosporins if they are inhibited by a MIC of 32 ug/ml or less. Using this definition, we have that one strain of *Pseudomonas aeruginosa* was resistant to cefoperazone, 3

strains were resistant to moxalactam, 16 strains were resistant to cefotaxime and 18 strains were resistant to ceftizoxime.

Cefoperazone was the most active agent against the 20 strains of *Pseudomonas aeruginosa* tested with an MIC₉₀ of 8 ug/ml. Moxalactam, cefotaxime and ceftizoxime had comparatively similar activity with an MIC₉₀ of 64 ug/ml.

Table I compares the results of the antibiotics interaction utilizing the FIC index and the definition of synergism, antagonism and indifference as presented in methodoloy. Results were similar, except that by FIC index criteria, antagonism was seen in one strain of *P. aeruginosa* when amikacin was combined with cefoperazone. The MIC of this strain to amikacin increased from 4 ug/ml to 8 ug/ml (FIC index=2.003). Utilizing the definition criteria, the combination amikacin-cefoperazone was indifferent against this same strain.

By both criteria, the antibiotic combination synergistic for the greatest number of strains was ceftizoxime-amikacin. Synergism as defined by FIC index was found in 85% with the combination of ceftizoxime and amikacin. The other three combinations were comparable in activity: 20% synergism when cefotaxime or cefoperazone was combined with amikacin and 15% synergism when moxalactam was combined with amikacin.

Results of mean MIC for each antibiotic used alone and in combination with amikacin against the 20 strains of *Pseudomonas aeruginosa* are presented in Table 2. When mean MICs are compared, it is observed that for cefoperazone, the mean MIC decreased onefold, from 5.6 ug/ml to 2.73 ug/ml after it was combined with amikacin. For ceftizoxime the mean MIC decreased from 43.2 ug/ml to 9.2 ug/ml (fivefold decrease); for moxalactam, it decreased from 21.69 ug/ml to 4.79 ug/ml (fourfold decrease); and for cefotaxime it decreased from 38.4 ug/ml to 12.03 ug/ml (threefold decrease).

In a previous comparison of synergy between B-lactam-tobramycin combinations, Mintz and Drew⁸

TABLE I

Results of antibiotic combinations against 20 strains of

Pseudomonas aeruginosa					
	Combinations				
		Cefoperazone Amikacin	Cefotaxime Amikacin	Moxalactam Amikacin	Ceftizoxime Amikacin
		No. of Strains (%)			
Synergism	FIC Index Definition	4 (20%) 4 (20%)	4 (20%) 4 (20%)	3 (15%) 3 (15%)	17 (85%) 17 (85%)
Antagonism	FIC Index Definition	1 (5%)	_	Ξ	Ξ
Indifference	FIC Index Definition	15 (75%) 16 (80%)	16 (80%) 16 (80%)	16 (80%) 16 (80%)	3 (15%) 3 (15%)
Equivocal	FIC Index Definition	Ξ	=	<u>1</u>	

F1C index and definition as described in methodology

TABLE II

Comparative in vitro activity of cefoperazone, cefotaxime, moxalactam, and ceftizoxime in combination with amikacin against 20 strains of Pseudomonas aeruginosa

	Antibiotic Alone	Antibiotic in combination		
Antibiotic	Mean MIC	Amikacin Mean MIC (ug/ml)	Cephalosporin Mean MIC (ug/ml)	
Cefoperazone	5.6	1.03	2.73	
Cefotaxime	38.4	1.25	12.03	
Moxalactam	21.69	1.44	4.79	
Ceftizoxime	43.2	1.56	9.2	
Amikacin	6.3	_	_	

reported comparable results for cefoperazone-tobramycin and moxalactam-tobramycin (12% + 18% respectively); they also described that the cefotaxime-tobramycin combination was more synergistic (63%).

Analysis of the present data is conflicting. The antibiotic combinations showing greater synergistic activity were the same ones which, paradoxically, were needed in higher concentrations as sole agents to inhibit the *P. aeruginosa* strains studied.

The combination of cefoperazone-amikacin demonstrated 20% synergism, with a mean MIC for cefoperazone as a single agent of 5.6 mcmg/ml, decreasing to 2.7 mcgm/ml when it was combined with amikacin. In contrast, while the combination ceftizoxime-amikacin demonstrated 85% synergism, the mean MIC for ceftizoxime alone was 43 mcgm/ml, and 9.2 mcgm/ml when it was combined with amikacin.

The appparent discrepancy of the *in vitro* activity of the antibiotics studied when their MICs and their synergistic activity was determined, may represent a test tube effect, and may not have any clinical significance. When we study antibiotics which have very low MICs for a particular group of strains it may be very difficult to find synergism as presently defined, but then we may have to question ourselves its clinical importance or its consequences.

While we do not have answers to all the above questions, we want to bring to the attention of the clinician that *in vitro* synergy may be confusing and misleading, and although it may serve as a guide to choose an antibiotic combination, it may need controlled clinical trials before we can safely say which is the best antibiotic combination to treat serious *P. aeruginosa* infections in the compromised host.

Acknowledgment

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We thank Mrs. Carmen D. Camareno for her excellent secretarial work.

Resumen: Se estudió la actividad in vitro de cefoperazone, cefotaxime, moxalactam y ceftizoxime individualmente y en combinación con amikacin en contra de 20 cepas de *Pseudomonas aeruginosa* obtenidas de la sangre de pacientes.

Ceftizoxime-amikacin resultó ser la combinación más sinergística (85%) utilizando el índice de la concentración inhibitoria fraccionada (FIC index). Sin embargo, si analizamos el efecto de la combinación de los antibióticos en la concentración mínima inhibitoria (MIC) en contra de Pseudomonas aeruginosa, la combinación más activa in vitro lo fue cefoperazone-amikacin. Esta aparente discrepancia en los resultados puede traer confusión si no entendemos las metodologías utilizadas y lo que cada una significa. Es nuestro interés alertar al clínico cuando utiliza el criterio de sinergismo para dirigir su terapia.

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its user may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in

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derived drugs.

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Precautions: The bipavailability of the hydrochlorothiazide component of

reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CD.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin (ACTH)). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, apranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak f

Thiazides may add to or potentiate the action of other antihypertensive

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toxicity.

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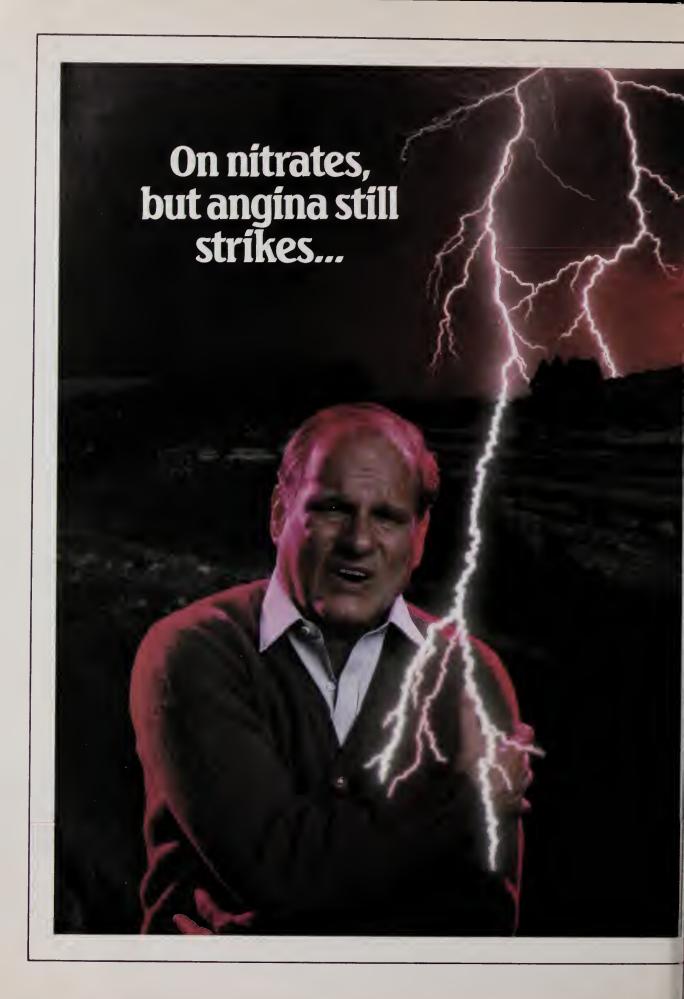
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ARTICULOS ESPECIALES

Mucocutaneous Lymphnode Syndrome or Kawasaki Disease*

Mucocutaneous lymphnode syndrome (MCLS) or Kawasaki disease (KD) is an acute febrile exanthema occurring mostly in infants and children. The first series of patients was reported by Kawasaki in 1967 in Japan. As the number of cases increased and the clinical picture became more widely recognized, reports of occasional deaths associated with Kawasaki disease, mostly from coronary vascular involvement, began to emerge. The autopsies from fatal cases soon demonstrated that the pathological findings were similar to those previously reported in the literature as "infantile periarteritis nodosa". One of Dr. Kawasaki's many contributions was to point out that a large number of patients with the same clinical picture do not die.

Because of the steadily increasing number of children being affected by Kawasaki disease in Japan and its possible ominous prognosis, a research committee was organized in that country in 1979, supported by the Ministry of Health and Welfare. Its purpose was to undertake epidemiological studies, to search out the cause and to examine different methods of treatment for the disease. Despite the efforts of this committee, the aetiology of the disease has not been elucidated. To date over 50,000 children have been afflicted with Kawasaki disease in Japan and the disease has also been encountered in many other countries.

Kawasaki disease is clinically characterized by:

- 1. fever of unknown aetiology lasting five days or more,
- 2. bilateral congestion of the ocular conjunctivae,
- 3. inflammatory changes of the lips and oral cavity,
- 4. acute non-purulent swelling of cervical lymph nodes,
- polymorphous exanthema of the torso, reddening and swelling of peripheral extremities with desquamation of the skin and.
- 6. most importantly, signs and symptoms of cardiovascular involvement including pancarditis, myocarditis, ECG changes, angina or infarction, arrhythmia, mitral regurgitation, tamponade, etc.

Pathologically Kawasaki disease is an acute inflammatory condition with systemic angiitis affecting capillaries and small and medium sized arteries. Thrombotic coronary aneurysm with or without other systemic artery involvement is usually present at autopsy. The disease has attracted much attention recently because asymptomatic coronary artery lesions may persist as sequelae in probably 10% of the patients, although in the majority such coronary changes appear to regress spontaneously following subsidence of the acute inflammatory reaction.

The Japanese epidemiological study group proposed a worldwide survey of Kawasaki disease in 1979. The result was that 12 different countries from North America, Europe and Asia responded by registering similar cases. Since then this disease has come to be recognized as a clinical entity not only in Japan but also worldwide. It is conceivable that children who have suffered Kawasaki disease, even those without manifest ischaemic sequelae, may be predisposed to obstructive coronary arterial disease in adult life. This possibility is of real concern for physicians, paediatricians and cardiologists as experience with the disease increases and two-dimensional echocardiography permits non-invasive detection of coronary artery dilatation lesions. So far most of the cases have occurred in so called industrialized countries and reports of Kawasaki disease are infrequent from developing nations. The possibility exists that, as such countries gradually become industrialized, Kawasaki disease may also appear in those regions of the world.

In 1982, the ISFC Scientific Council on Paediatric Cardiology (Chairman: Dr. Luc Van der Hauwaert), formed an international committee on Kawasaki disease, co-chaired by Drs. Atsuyoshi Takao (Japan) and Richard D. Rowe (Canada). Other committee members include Drs. Hirohisa Kato, Tetsuro Kamiya and Sanji Kusakwa (Japan), Welton Gersony (USA), Choompol Vongprateep (Thailand) Luc Van der Hauwaert (Belgium), Asuquo Antia (Nigeria) and Fause Attie (México). A questionnaire was widely distributed through the regional committee members to medical specialists in their geographical region. The data are currently being examined and will be presented at the 2nd World Congress of Paediatric Cardiology (New York, 2nd-6th June 1985). Recommendations for further action by the Council on Paediatric Cardiology will be made shortly.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



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In niño de 2 años de edad es hospitalizando electivamente para estudios diagnósticos. Los datos significativos en su historial médico pasado son: episodios de cianosis transitoria en la primera semana de vida, soplo cardíaco a los dos meses de edad y pobre aumento de peso. También informan de infecciones de vías respiratorias altas frecuentes. No hay evidencia de fallo cardíaco congestivo ni de cianosis.

Al examen físico se aprecia un niño distrófico, acianótico, con signos vitales normales. El precordio está "tranquilo", no hay accesibilidad ventricular y los sonidos cardíacos son buenos. Hay un soplo pansistólico "crescendo", rudo, grado 3/6 que se aprecia mejor en los espacios intercostales 2 y 3 a lo largo del reborde esternal izquierdo. Se irradia al hemitorax derecho superior y espalda sin componente diastólico. El S₁ es normal, el S₂ se desdobla bien, aunque con un P₂ acentuado. Los pulsos periféricos son fuertes, pero no "saltones". No hay visceromegalia. La Hb, ECG y radiografía de tórax son normales.

Por cineangiocardiografía se obtiene la imagen que se ilustra a continuación:



Figura 1. Aortograma retrógrado que confirmó el diagnóstico en el paciente.

AA-aorta ascendente, AV-valvula aórtica, MPA-arteria pulmonar, LPA-arteria pulmonar izquierda, RCA-arteria coronaria derecha, LCA-arteria coronaria izquierda.

Ventana Aorto-pulmonar

El septo espiral aorto-pulmonar se fusiona temprano en el embrión, quedando así separada la aorta de la arteria pulmonar. Cuando ocurre un fallo en este proceso queda una comunicación entre los dos grandes vasos distal al origen de sus válvulas. A este defecto se le ha llamado: ventana aorto-pulmonar, defecto septal aortico-pulmonar y fenestración aorto-pulmonar. El término tronco arterioso parcial ya no se utiliza.

La ventana aorto-pulmonar es una anomalía cardíaca poco frecuente. En el Hospital de Niños de Toronto se han descrito sólo 23 casos de un total de 15,100 niños en un período de 23 años. 1 El defecto suele tener forma redonda u ovalada y es por lo regular de tamaño grande. Está localizado entre el lado izquierdo de la aorta ascendente y la pared derecha adyacente de la arteria pulmonar principal, justo antes del origen de la rama derecha pulmonar. Esta es la localización más frecuente y constituye el tipo I según la clasificación de Richardson² y la de Mori.³ Aquellos defectos más distales y que envuelven el origen de la arteria pulmonar derecha se clasifican como tipo II. El defecto tipo III de Mori incluye todo el lado derecho del tronco pulmonar, desde el área supravalvular hasta el área de la bifurcación pulmonar y el segmento proximal de la arteria pulmonar derecha. Según Richardson, el tipo III es aquel donde la arteria pulmonar derecha se origina de la aorta ascendente. Sin embargo, este último defecto es considerado por algunos como un hemitronco. 4 En los defectos aorto pulmonares las dos válvulas semilunares están presentes, lo que ayuda a diferenciarlos del tronco arterioso persistente.

Usualmente la ventana-pulmonar ocurre de forma aislada pero puede asociarse a otras cardiopatías como: la comunicación interventricular, el ducto arterioso patente, tetralogía de Fallot, defectos interatriales tipo secundum y particularmente la interrupción del arco aórtico. Esta última anomalía está muy frecuentemente

asociada a la ventana aorto-pulmonar.5

Clínicamente este defecto puede expresarse de diversas formas, dependiendo del tamaño del defecto, la magnitud y dirección del corto circuito, la resistencia pulmonar, la edad del paciente y la existencia de cardiopatías asociadas. Es común en estos niños un desarrollo somático lento, una mayor incidencia de infecciones de las vías respiratorias altas y fallo cardiáco en los primeros meses de vida. En muchas ocasiones, como lo fue nuestro caso, no hubo un curso clínico tan problemático.

Al examen físico suele estar presente un soplo que puede ser sistólico-eyectivo o contínuo a lo largo del margen esternal izquierdo superior. El segundo sonido (S₂) por lo regular está estrechamente desdoblado, con un componente pulmonar (P₂) acentuado y en los pacientes con resistencia pulmonar elevada puede haber cianosis discreta. Los pulsos periféricos son de mayor amplitud que lo usual o ser obviamente "saltones". Se debe tener en mente sin embargo, que un 10% de los pacientes con ventana aorto-pulmonar pequeña tienen un curso clínico totalmente asintomático. En ellos el primer signo suele ser la presencia de un soplo inespecífico en un examen médico de rutina.

El electrocardiograma puede ser normal o presentar hipertrofia ventricula izquierda discreta. La radiografía de toráx puede demostrar cardiomegalia variable, según el tamaño del defecto y la resistencia pulmonar. Lo mismo puede decirse de la circulación pulmonar. Cuando el corto circuito de izquierda a derecha a través del defecto es significativo (>2:1), puede a preciarse eviden-

cia radiográfica de dilatación atrial izquierda.

El defecto septal aortico-pulmonar se debe diferenciar del ducto arterioso patente y del tronco arterioso persistente. La mayoría de las veces solo puede lograrse por medio del cineangiograma. Para confirmar el diagnóstico se necesita demostrar la presencia de dos válvulas semilunares, lo que permite diferenciarlo de un tronco arterioso persistente. Con el aortograma también puede demostrarse que la comunicación aorto-pulmonar está localizada en la aorta ascendente y no en la descendente, como sucede en el ducto arterioso patente. En la figura l se puede apreciar el "chorro" de material de contraste pasando desde la aorta ascendente a la arteria pulmonar através de la ventana aorto pulmonar. La flecha señala la comunicación aortopulmonar.

El tratamiento de esta cardiopatía congénita poco frecuente consiste de sutura o de división de la fenestración, tal como se hace con el ducto arterioso patente. La preferencia de una técnica sobre la otra depende en gran medida de la localización y tamaño del defecto con relación a la aorta y las arterias coronarias. Con excepción del neonato con cardiopatías asociadas y fallo cardíaco severo, los resultados del tratamiento quirúrgico son excelentes. 6 Con los avances de la cirugía cardíaca en infantes se ha logrado manejar estos pacientes (que antes se consideraban de pobre riesgo operatorio) con gran éxito a corto y a largo plazo.

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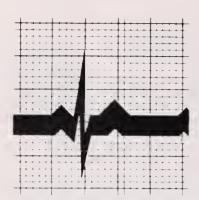
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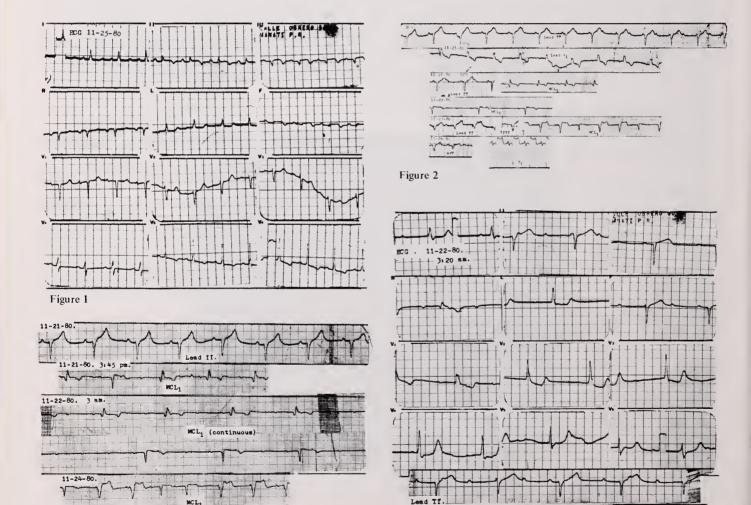
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ELECTROCARDIOGRAM OF THE MONTH

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Electrocardiographic principles underlie our interpretation of the basic electrocardiogram (ECG) and complex arrhythmias. The following patient provides a host of clinical and interpretive challenges and education for the practitioner and diagnostician managing a patient with an acute myocardial infarction (AMI).



This 69-year-old female was admitted to the Coronary Care Unit (CCU) with chest pain of one week duration. Cardiac enzymes were elevated. An ECG from 1979 was normal.

Figure 4

Figure 3

An ECG four days after admission, Figure 1, showed an acute inferior myocardial infarction (AIMI) and lateral ST-T wave abnormalities.

Figure 2 shows a composite of arrhythmias manifested over a 4-days period. On admission, 11-21-80, leads II and V_1 showed right bundle branch block (RBBB) and left anterior hemiblock (LAH)- a bifascicular block. The atrial (P) rate (AR) = 108 per minute (sinus tachycardia and arrhythmia), and the ventricular rate (QRS), VR, = 54-55. The P-R distances shorten, indicating atrioventricular (AV) dissociation (AVD), but there is another P wave which emerges from the T waves. Atrial overload is evident. CCU tracings- the P (near 104) and QRS (51-53) rates vary within a few ms. Q/S complexes are present in MCL₁ and the V_1 lead above. P-R distances changes slightly in MCL₁. VR is 50. Diagnoses are Block-Dissociation (B-D), as 2:1 AV block (AVB) with AVD. No ventriculophasic phenomenon (Erlanger-Blackman) was present.

On 11-20-80, the P rate was about 93 and the QRS 30. The P-R interval is fixed at 0.32 S. This represents 3:1 AVB (due to concealed conduction or multilevel AVB) and first-degree AVB of the conducted beats, Type B (<0.12 S) AV nodal/His bundle (HB) block.

11-23-80 - P rate 90; Paced beats, of QS morphalogy, at 72. The third (P-R 0.27 S and R-P 550 ms) and sixth (P-R 0.20 S and R-P 640 ms) beats are sensed sinus conducted beats with reciprocal R-P/P-R relationships - pacemaker escape-capture trigeminy.

11-24-80 - In aVF the first beat may be paced, and the second a sinus and pacemaker fusion beat; spike-Qr. The monitor lead on the following day showed normally conducted sinus rhythm.

Figure 3. Also 11-21-80. The P-R interval is fixed at 0.20 S (until the last beat of P-R distance 0.18 S), compatible with 2:1 AVB, the blocked P falling in the T wave. P 112, QRS 56.

The MCL_1 strip shows sinus tachycardia of 115-118. The third P wave captures the second QRS complex with basic morphology at a P-R interval of 0.31 S. Artifact. The regular Q/R complex, rate 52, appears dissociated from the sinus impulses.

On 11-22-80, the Prate was 88-92 and the bizarre broad Q/R complex 35.7-36.8 in the upper of the continuous strips. Then a long ventricular pause of 4.49 S ensued as complete AVB and ventricular asystoledepressed automaticity in the His-Purkinje system (HPs) or repetitive discharge of automatic fibers by concealed conductionterminated by 3:1 AVB (P-R of the conducted beats 0.32 S, identical to the sinus conducted beats of Figure 2) and with the basic QRS morphology, with out RBBB. Trifascicular block (TB) was likely, but no phase 4 AVB. The MCL₁ strip of 11-24-80 showed ventricular paced beats with rate of 71-72 (second, third, sixth and seventh), and sinus captured beats (first, fourth, fifth and eighth) with P-R intervals of 0.24 and 0.30 S (Wenckebach sequence) and 0.18 S, and R-P intervals of 520, 360 and 824 ms, respectively-reciprocal relatioships; the P rate is 93-94.

Figure 4. P near 92, VR 40.4. RBBB and LAH pattern. The beat in V₃ comes slightly early. "Almost complete AVB" and complete AVD.

Discussion

RBBB Plus LAH

These complicate AMI in 5% of cases and is the most common intraventricular conduction defect presaging complete AVB, which ensues in 33-46% of these patients with a 45% mortality. AMI, RBBB and a Q/QR in lead V₁ are predictive for the development of complete AVB and thus merit temporary pacing. They reflect a proximal occlusion of the left anterior descending coronary artery (LADCA) which provides blood to the right bundle branch (BB) and the left anterior fascicle. This data refers especially to acute anterior MI which has the reputation of: 1) bilateral infra-His Mobitz II bundle branch block (BBB) or TB, 2) preceding RBBB + LAH or alternating BBB; the latter causes a wide QRS complex prior to inducing a high degree AVB (HDAVD), 3) a normal or slightly prolonged P-R interval, 4) the sudden onset of complete AVB with unstable, broad, bizarre multiform QRS patterns at a rate of 20-40 per minute and, 5) a mortality of 75%, indicating excess mortality and morbidity.

AIMI

The mortality in AIMI is 12%, but high grade and complete AVB (15% incidence of this and second degree AVB) augment it to 20-50% reflecting a greater amount of myocardial ischemia, injury and necrosis of the AV node and proximal HB, increased vagal tone, a prior history of MI and higher incidence of severe complications. The AV nodal artery (in 95% of cases it arises from the right CA) provides vascularity to the diaphragmatic surface of the left ventricle, the AV node and proximal right and left BBs. AIMI usually progresses slowly to complete AVB via first degree and Wenckeback block, manifesting markedly prolonged P-R intervals, normal width idiojunctional escape beats at a rate of 40-60, and is transient lasting hours or days. 1-5

IMI versus LAH

LAH may mask or mimic IMI. LAH produces deep rS complexes in leads II, III and aVF; the r is retained because the initial inferior vector is unaffected as LAH spares the posterior region of the inferior wall. There are a terminal r wave in aVR and a counterclockwise (ccw) frontal loop. IMI shows Qr/QR complexes in II, III and aVF and not so deep S waves; a late R (inferior, rightward vector) wave tends to exclude LAH. The frontal VCG loop is clockwise (cw) and initially superior. Both in the same patient produces a leftward, superior cw loop for 20-30 ms, which then goes ccw superiorly for the delayed terminal 40 ms vector; the maximal QRS deflection is in the left superior quadrant above the X axis. There may be deep QSs in II, III and aVF, and a Q of any magnitude in II; the peak of the terminal R wave in aVR occurs later than the terminal R in aVL.1, 6-10

BBB In AIMI

RBBB occurs in 5.2% or more of IMI patients. In complete AVB complicating IMI the escape is usually

junctional or Hisian, revealing normal width beats. In the past, BBBs and hemiblocks were believed to be rare in this context. However, an AIMI occasionally extends to the septum involving the BBs. Junctional escape beats may be conducted aberrantly due to functional dissociation in a BB, a preferential pathway such as a Mahaim tract, supernormal intraventricular conduction, Wedensky facilitation or most likely phase 4 depolarization. Escape beats that are 0.12 S or more broad, more often of RBBB pattern than left BBB, occur occasionally and were considered to carry a high mortality. Castellanos stated that infranodal conduction defects in AIMI have the same significance as those of acute anterior MI (80%). Yet Lie et al found width and frequency of no prognostic significance.⁵, ¹¹

A normal QRS width manifests in conducted beats. Wide QRS complexes in AIMI with complete AVB may be explained by: 1) a prior existent BBB (mortality same), 2) Lenegre and Lev's diseases, 3) a ventricular escape rhythm from acute bilateral BBB or TB (mortality higher), 4) an idiojunctional rhythm with LAH which occurs in up to 39-46% of cases, 5) two-vessel disease involving both the right CA and and LADCA; 6) previous collateralization resulting in more extensive blood supply to the septum via short septal perforators from the posterior descending CA; 7) vascularization of the HB and proximal BBs via the AV nodal artery; 8) If no BBB manifests in the sinus beats, but there are wide escapes during heart block, most likely there is block in the HB which has a variable prognosis.

This patient's RBBB, and Q/R complexes may be due to double AV junctional and BBBs: 1) AV nodal + upper HB disease producing the 3:1 and 2:1 AVBs, the distal HB escape rhythm conducted with RBBB and LAH; 2) a left ventricular proximal posterior fascicular focus (Fascicular rhythm), which is slower, without complete RBBB and is similar; 3) or two foci. When the nodal rhythm in 2:1 AVB is very slow, a fascicular escape must be considered.

2:1 AVB + RBBB can be induced by, 1. a 2:1 AV nodal block + third degree block in one BB, 2. 2:1 AV nodal block + unequal first degree bilateral BBB, and 3. 2:1 left BBB + third degree RBBB. The subsequent complete AVB with a broad Q/R escape rhythm or ventricular standstill probably signifies acute TB with a distal left ventricular Purkinje or absent escape rhythm. 1, 4, 5, 11-13, 13_b

2:1 AVB

This can represent either Mobitz I or II block. Mobitz I block would be supported by: Wenckebach block in other portions of the trace, normal width QRS, variable and prolonged P-R intervals of sinus conducted beats, improvement with exercise and shortening of the P-R interval after a blocked impulse. Mobitz II shows a wide QRS (Type B block), a normal fixed P-R interval, a fixed P-R of a capture beat, unstable infranodal worsening on exercise and H potential after the blocked P wave. An escape beat would be identified by P-R shortening after a blocked P wave. 2:1 + a BBB may reflect block in the AV node or in the HPs. 12-15

B - D. 2:1 AVB + AVD

AVD means independent beating of the atria and ventricles. Interference refers to physiological collision of electrical wave fronts, or to a ventricular capture beat. Escape rhythms frequently complicate 2:1 or HGAVB and long periods of AVD transpire mimicking complete AVB (false complete AVB, pseudointermittent complete AVB, almost complete AVB), either nodal or infranodal. The blocked impulse results in a long ventricular pause. which if longer than a potential AV anodal or ventricular escape cycle, permits an escape beat (junctional or ventricular) to appear. The escape occurs before the sinus impulse can activate the ventricles. The blocked P is due to pathological AV nodal refractoriness and block, while the other second P wave (previously conducted) is now nonconducted because of the normal nodal or HP refractoriness created by retrograde conduction of the dissociated idiojunctional or ventricular beat. The VR > 1/2 the AR (2 x P-P interval). Castellanos explains that this can end if: 1) the 2:1 AVB changes into a Wenckebach block with varying ratios, 2) the sinus rate speeds up and the A wave precedes the His beat, or 3) the automaticity of the HB pacemaker decreases providing the corresponding sinus impluse enough time to activate the ventricles. It has been stated that the VR must be 35-40 before the diagnosis of complete AVB can be made, because the escape focus may be accelerated! In HDAVB the AR is faster than the VR, and thus some degree of AVB, but not 1 necessarily complete, must be present. If AVB were not present conducted sinus rhythm would ensue. B-D is particularly characteristic of AIMI, digitalis intoxication and the postoperative state. 12, 16-23

3:1 AVB

HDAVB (advanced) means the block of two or more consecutive supraventricular impulses at a rate of 140 or less. 3:1 AVB is a form of HDAVB and is rare as are odd ratios. It is more common in Mobitz II (3:2) but it may result from concealed conduction of the first nonconducted sinus impulse in 3:2 AV Wenckebach (abortive attempt at 3:2) conduction. This concealed sinus impulse penetrates deeply and variably into the AV junction altering the refractory period so that the next atrial impulse is blocked. Also, it can be produced by concealed ventriculoatrial conduction from ventricular ectopy in 2:1 AVB. It can occur intermittently during rhythms with varying AV nodal block. HDAVB may occur in the AV node (suggested by an IMI, digitalis, B-blocker, verapamil, a narrow QRS complex in conducted beats, prior Wenckebach conduction and reversion to 1:1 conduction after atropine), in the HB, and in the BB-P system (absent history of the above drugs, BBB or bifascicular block in conducted beats and no change or increase in conduction ratio on acceleration of sinus rate after atropine).3, 12, 17-19

More recently, 3:1 AVB has been explained by the concept of multilevel AVB due to differential refractoriness at multiple levels in the AV junction. An effective 3:1 AVB at the ventricular level thus results from a differential triple level or double level block (Type B

mechanism 2) as: upper 3:2 Wenckewbach block, mid 2:1 AVB and lower 1:1 AV conduction. 12, 19, 24

Rate - Dependent Block

All the QRS patterns except the broad Q/R complexes appear to have been sinus conducted and supraventricular. Analysis of the ARs, VRs, the 2:1 AVB with and without AVD, the 3:1 AVB without RBBB + LAH, the complete AVB with Q/R escape rhythm and the Wenckebach conduction, forces a consideration of phase 3 or 4 block (accordion, "muelle") or gap phenomena. Evidence for these is not strong except for possible phase 3 infranodal block. 14, 25-27

Other Differential Diagnostic Considerations

These comprise: 1) AVD alone; Incomplete Interference AVD; 2) 2:1 synchronization in AVD and complete AVB; 3) Atypical Wenckebach block; 4) Reverse Wenckebach (Berman); 5) second degree Type B 2:1 block with alternating P-R intervals. 12, 14, 21, 23, 25-27 Cardiac electrophysiological studies would have been of considerable value in approaching these differential diagnoses.

Diagnosis of AMI During Permanent Pacing

Ventricular pacing may mimic or mask a MI, and almost always masks IMI by producing QS complexes in the inferior leads (occasionally a tiny r wave is present). However, the ECG diagnosis of AMI during nonprogrammable permanent pacing may be possible by: 1) Analysis of any intrinsic rhythm, "infarct extrasystole", supraventricular tachycardia or escape beats, suppression of a VVI pacer by chest wall stimulation, etc; 2) serial evolving primary ST-T wave abnormalities of injury and ischemia; but ST depression and T inversion and pseudocurrents of injury can occur secondary to pacing itself. 3) a spike-qR pattern in leads I, aVL, 5₅₋₆ of extensive anteroseptal MI during right ventricular (RV) apical paicing. 4) initial or intermediate R, rS in aVR; 5) possibly, marked anterior displacement of the horizontal loop in dorsal MI; 6) QR, Qr, qR paced beats in leads II, III and aVF, and a cw frontal loop with late afferent activation oriented inferiorly. This is not seen in uncomplicated pacing from anywhere in the RV.28, 29

Indications For Pacemakers

B-D in its sundry apparitions (2:1 + AVD) is consistently misdiagnosed as complete AVB leading to unnecessary pacemaker placement. B-D, particularly if an end result of Mobitz I, does not necessarily indicate a pacemaker; monitoring and supportive care may be sufficient. In AIMI and complete. AVB, mortalities with and without pacing were similar. Routine pacing may not be indicated but pacing is needed on several indications: 1) Stokes-Adams attacks, symptoms; 2) hypotension, power failure with shock; 3) bradycardiadependent ventricular arrhythmias, or to overdrive arrhythmias; 4) HDAVB or a VR less then 45-50, and with wide escape rhythms; 5) for 2:1 AVB in the AV node, a pacemaker is not indicated if the patient is asymptomatic, if the block is druginduced or if the VR

increases after atropine, isoproterenol or during exercise; 6) It is indicated if there are symptoms, congestive heart failure, and if the VR<40 without appreciable increase after atropine or exercise. If hypotension and low cardiac output persist, an AV sequential pace may prove more beneficial. A temporary pacer is indicated for new RBBB + LAH. 7) Permanent pacing appears indicated for acute RBBB + LAH with (or perphaps without) transient HPs second or third degree AVB, in that only 10-65% of cases developed recurrent AVB or sudden death within the subsequent year compared to 65-100% without permanent pacing (anterior MI); death is due to AVB or ventricular fibrillation, 8) Permanent pacing is controversial in AIMI plus transient complete AVB without BBB.²⁻⁵, ²⁰, ²¹ Therefore, both temporary and permanent pacing were appropriate in the described patient.

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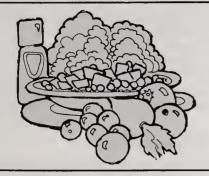
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MEDICAL ASPECTS OF NUTRITION

Osteoporosis*

steoporosis, a major public health problem, affects all bones, typically the spine, wrist and hip. Risk of developing osteoporosis increases with age, is higher in women than men and in whites blacks. Its cause appears to reside in the mechanisms underlying an accentuation of the normal loss of bone, which follows menopause in women and occurs in all individuals with advancing age. There are no laboratory tests for defining individuals at risk or those with mild osteoporosis. Diagnosis is established by documentation of reduced bone density with a typical fracture syndrome after exclusion of known causes of excessive bone loss. Prevention of fracture in susceptible patients is the primary goal of intervention. Strategies include estrogen replacement in postmenopausal women, adequate nutrition, including an elemental calcium intake of 1,000-1,500 mg/day, and a program of modest weight-bearing exercise. There is great need for additional research on understanding the biology of human bone, defining individuals risk and developing safe, effective, low-cost strategies for fracture prevention.

What is Osteoporosis?

Primary osteoporosis is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss.

Osteoporosis affects as many as 15-20 million individuals in the U.S., attributing to 1.3 million fractures annually in people age 45 and older. The cost of osteoporosis in the U.S. has been estimated at \$3.8 billion annually.

Bone is composed of a collagen-rich organic matrix impregnated with mineral-largely calcium and phosphate. Two major forms of bone exist: compact cortical bone forms the external envelopes of the skeleton; trabecular or medullary bone forms plates that traverse the internal cavities of the skeleton. The proportions of cortical and trabecular bone vary at different sites. Vertebral bodies contain predominantly trabecular bone, while the proximal femur contains predominantly cortical bone. The responses of the two forms of bone to metabolic influences and their susceptibility to fracture differ.

Bone undergoes continuous remodeling throughout life. Osteoclasts resorb bone in microscopic cavities; osteoblasts then reform the bone surfaces, filling the cavities. Normally, bone resorption and formation are linked closely in space, time and degree. Mechanical and electrical forces, hormones and local regulatory factors influence remodeling.

Peak bone mass is achieved at about 35 years of age for cortical bone and earlier for trabecular bone. Sex. race. nutrition, exercise and overall health influence peak mass. Bone mass is approximately 30% higher in men than in women and approximately 10% higher in blacks than in whites. In each group, bone mass varies among individuals. After reaching its peak, bone mass declines throughout life due to an imbalance in remodeling. Bones lose both mineral and organic matrix but retain their basic organization. In women, bone mass decreases rapidly for 3-7 years after menopause. Bone loss also is enhanced in a variety of diseases. Women have more fractures than men and whites have more fractures than blacks. Three factors determine the liklihood of fractures: (1) the magnitude, direction and duration of the applied force; (2) the dissipation of that force by muscle contraction and soft tissue absorption; and, (3) bone strength. Injuries are more frequent and energy dissipation diminishes with advancing age. Reduction in bone mass in the most important reason for the increased frequency of bone fracture in postmenopausal women and in the elderly.

Classifying primary osteoporosis into clinical, histological or biochemical subsets may be useful from the standpoint of etiology, prevention and treatment. There is clinical and histological evidence for different subsets. Vertebral fractures occur most often in women aged 55-75 with accelerated loss of trabecular bone. Hip fractures occur most frequently in older men and women who slowly have lost both cortical and trabecular mass. Bone

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biopsies from some individuals with primary osteoporosis show high turnover rates; biopsies from others show low or intermediate rates of turnover.

Clinical Features of Osteoporosis

Clinical manifestations of osteoporosis include fractures and their complications. Characteristically, fractures occur in the thoracic and lumbar vertebral bodies, the neck and intertrochanteric regions of the femur and the distal radius. Osteoporotic individuals may fracture any bone more easily than their nonosteoporotic counterparts.

Vertebral compression fractures occur more frequently in women than in men and typically affect T₈-L₃. These fractures may develop during routine activities, such as bending, lifting or rising from a chair or bed. Immediate, severe, local back pain often results. Pain usually subsides within several months. Some individuals experience persistent pain due to altered spinal mechanics. In contrast, some vertebral fractures do not cause pain. Gradual asymptomatic vertebral compression may be detected only upon radiographic examination. Loss of body height and/or the development of kyphosis may be the only signs of multiple vertebral fractures. Discomfort, debility and, rarely, pulmonary dysfunction may accompany thoracic shortening. Abdominal symptoms may include early satiety, bloating and constipation.

Hip fractures are another important manifestation of osteoporosis. The affected population tends to be older and the sex distribution more even than is the case in vertebral fracture. Acute complications—hospitalization, depression and mechanical failure of the surgical procedure—are common. Most patients fail to recover normal activity and mortality within 1 year approaches 20%. Distal radial fractures limit use of the extremity for 4-8 weeks, although long-term disability is uncommon. These fractures promote fear of loss of independent living, fear of additional falls and fractures and depression.

Detection of low skeletal mass and/or a fracture after minor trauma should alert the physician to the presence of metabolic bone disease and to evaluate further to exclude osteomalacia, hyperparathyroidism, hyperthyroidism, multiple myeloma, metastatic disease, syndromes of glucocorticoid excess and other causes of secondary osteoporosis. No blood or urine test establishes specifically the diagnosis of primary osteoporosis but such tests may exclude secondary causes.

Several noninvasive methods are available to evaluate bone density, varying widely in cost, availability and radiation dose. Roentgenograms are, however, insensitive indicators of bone loss since bone density must be decreased by at least 20%-30% before the reduction can be appreciated. Characteristic abnormalities on standard roentgenograms are sufficient for establishing diagnosis of osteoporosis if secondary causes are excluded clinically or radiographically. If the spine film is not diagnostic but clinical suspicion is high, a variety of other procedure may be indicated. These include radiogrammetry for measurement of cortical thickness, photodensitometry, the Singh Index of femoral trabecular pattern, single and dual photon absorptionmetry, neutron activa-

tion, Compton scattering and single and dual energy computed tomography. Use of these techniques will depend on their availability, cost and further studies of their discriminatory capabilities and sensitivity. With histomorphometry, usually performed on a bone biopsy form the iliac crest, bone mass can be evaluated and osteomalacia and certain forms of secondary osteoporosis excluded. Bone biopsy is safe but requires specialized equipment and expert analysis that are not widely available.

Who Is At Risk?

Bone mass declines with age in all people and is related to sex, race, menopause and body weight-for-height. Women ar at higher risk than men because they have less bone mass than men and for several years following menopause, the rate of bone mass decline is accelerated. Early menopause is one of the strongest predictors for the development of osteoporosis. Women who are underweight also have osteoporosis more often than overweight women. Cigarette smoking may be an additional predictor of risk. Calcium deficiency has been implicated in the pathogenesis of this disease.

Immobilization and prolonged bed rest produce rapid bone loss, while exercise involving weight bearing has been shown to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that will prevent osteoporosis have not been established. Exercise sufficient to induce amenorrhea in young women may lead to decreased bone mass. The relationship of osteoporosis to hereditary and dietary factors, such as alcohol, vitamins A and C, magnesium and protein, is less firmly established. Some of these factors may act indirectly through their effect on calcium metabolism or body weight.

Possible Causes of Osteoporosis

Because primary osteoporosis is characterized by decreased bone mass, the causes of the disorder must be sought among the factors that determine the quantity and quality of bone, including the magnitude of maximum bone mass at maturity and the rate of bone loss with aging. Complex cellular, physiologic and metabolic factors may underlie the pathogenesis of osteoporosis. Discrete cell types, anatomically and functionally connected, are continually renewed and maintain the complex skeletal tissue. Several systemic hormones and an increasingly recognized number of local (paracrine) factors regulate bone cell activity. Diet, as well as intestinal and renal function, influences mineral ion homeostasis needed to maintain the skeleton. Formation and resorption of bone and their coupling also are modified by external physical forces, such as those generated by body weight and exercise.

Osteoporosis is histologically, biochemically and kinetically, heterogeneous; rapid bone turnover or reduced rates of bone formation have been documented in patients with primary osteoporosis. Multiple etiologies would not be surprising, considering the complex factors regulating normal bone metabolism. Among the many possible etiologies of primary oster porosis, current data

point to two probable causes: deficiency of estrogen and deficiency of calcium. Rapid bone loss often accompanies menopause and premature osteoporosis follows bilateral oophorectomy. Estrogen replacement prevents bone loss in both conditions. The following observations support a causal ralationship between calcium deficiency and osteoporosis: calcium deficiency in experimental animals causes osteoporosis; a low calcium intake is common among the elderly in the U.S.; and, calcium supplementation reduces bone loss.

Prevention and Treatment

Physicians must emphasize measures that retard or halt the progress of osteoporosis before irreversible structural defects occur. The mainstays of prevention and management of osteoporosis are estrogen and calcium; exercise and nutrition may be important adjuncts.

Estrogen replacement therapy is highly effective for preventing osteoporosis in women. Estrogen reduces bone resorption and retards of halts menopausal bone loss. Case-controlled studies have shown a substantial reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass but does not restore it to premenopusal levels. Oral estrogen protects at low doses, such as 0.625 mg of conjugated equine estrogen, (25 micrograms of mestranol and 2 mg of estradiol valcrate daily exemplify other protective regimens reviewed by the panel).

All of the above data on efficacy are based almost exclusively on studies in white women. Therefore, the following recommendations on therapy for osteoporosis pertain to that group. Cyclic estrogen therapy should be given to women whose ovaries are removed before age 50 in whom there are no specific contraindications. Women who have had a natural menopause also should be considered for cyclic estrogen replacement if they have no contraindications and if they understand the risks and agree to regular medical evaluations. The duration of estrogen therapy need not be limited. There is no convincing evidence that initiating estrogen therapy in elderly women will prevent osteoporosis. The decision to treat women of other racial backgrounds should be determined on a case-by-case basis.

Estrogen-associated endometrial cancer is usually manifested at an early stage and is rarely fatal when managed appropriately. The bulk of evidence indicates that estrogen use is not associated with an increased risk of breast cancer. Adding a progestogen probably reduces the risk of endometrial cancer, but there is little information about the safety of long-term combined estrogen and progestogen treatment in postmenopausal women. Younger patients receiving progestogens in oral contraceptives experienced an increased risk of hypertension and cardiovascular disease. Some progestogens may blunt or eliminate the favorable effects of estrogen on lipoproteins. Until more data on risks and benefits are available, physicians and patients may prefer to reserve estrogen (with or without progestogen) therapy for

conditions that confer a high risk of osteoporosis, such as occurrence of premature menopause.

The usual daily intake of elemental calcium in the U.S.. 450-550 mg falls well below the National Research Council's (NRC) recommended dietary allowance (RDA) of 800 mg designed to meet the needs of approximately 95% or more of the population. Calcium metabolic balance studies indicate a daily requirement of about 1,000 mg of calcium for premenopausal and estrogentreated women. Postmenopausal women who are not treated with estrogen require about 1,500 mg/day for calcium balance. Therefore, the RDA for calcium is evidentally too low, particularly for postmenopausal women and may well be too low in elderly men. In some studies, high dietary calcium suppresses age-related bone loss and reduces the fracture rate in patients with osteoporosis. It seems likely that an increase in calcium intake to 1,000-1,500 mg/day beginning well before the menopause will reduce the incidence of osteoporosis in postmenopausal women. Increased calcium intake may prevent age-ralated bone loss in men as well.

The major sources of calcium in the U.S. diet are milk and dairy products. Each 8-ounce glass (240 ml) of milk contains 275-300 mg calcium. Skim or low fat milk is preferred to minimize fat intake. For those unable to take 1,000-1,500 mg calcium by diet, supplementation with calcium tablets is recommended, with special attention to their elemental calcium content.

Normal levels of vitamin D are required for optimal calcium absorption. Requirement for vitamin D increases with age. Persons who do not receive adquate daily sunlight exposure, such as those confined to home or to a nursing facility, are at special risk for vitamin D deficiency. Vitamin D has dangerous effects at high doses. Although the toxic dose varies among individuals, toxicity has occurred at levels as low as 2,000-5,000 I.U. daily. No one should consume more than 15-20 micrograms (600-800) units, twice daily RDA) without a doctor's recommendation.

Inactivity leads to bone loss. Some recent studies suggest that weight-bearing exercise may reduce bone loss. Modest weight-bearing exercise, such as walking, is recommended. Strategies to prevent falls are important in elderly patients who may fall frequently for a variety of reasons, such as from effects of drugs. Specific environmental interventions can minimize home hazards that increase the chance of falling.

Directions for Research

Future research in osteoporosis should approach the currently unanswered research questions concerning the development and maintenance of bone as a tissue, clinical and epidemiological research for practical prevention and treatment of the disease, factors controlling bone cell activity, regulation of bone mineral, and matrix formation and remodeling. This understanding will permit a more rational choice and evaluation of therapies, even as current treatments are evaluated clinically.

A Review of the Symposium* "Diet and Behavior— A Multidisciplinary Evaluation

Diane H. Morris, Ph.D., R.D.**
A Harold Lubin, M.D.

In the broadest sense, behavior can be defined as the response of an organism to its environment. For an organism as developmentally sophisticated as a human being, the nature of these responses is complex and often poorly understood. One factor that has the potential to affect human behavior is diet, which includes the variety, pattern, quantity and combination of foods and beverages consumed.

Because the relationship between diet and behavior is an emerging area of scientific investigation and public concern, a symposium "Diet and Behavior: A Multidisciplinary Evaluation" was sponsored by the American Medical Association, the International Life Sciences Institute and The Nutrition Foundation, Inc., on November 27-29, 1984 to: 1) examine the existing data related to the effect of diet on behavior; 2) discuss and evaluate methodologies for the assessment of behavior, nutrient intake and their interactions; and, 3) recommend strategies for improving research related to diet and behavior. This report reviews the major issues discussed in the symposium's three sessions.

I. Effects of Foods and Nutrients on Brain Function

The brain consists of a vast network of neurons that communicate with each other via the release of neurotrasmitters; the integration of this network, along with the spinal cord, forms the central nervous system and produces the complex phenomenon called behavior.^{1, 2} As many as 40 compounds that function as neurotransmitters have been identified. Most neurotransmitters are nitrogenous compounds derived from dietary protein.³

Numerous factors may affect neurotransmitter synthesis, including the availability of precursor compounds from the diet and thus from the bloodstream,³ the availability of vitamins and minerals for use as cofactors in biosynthetic processes or in the conduction of nerve impulses,¹ and the control of nutrient and precursor transport across the blood brain barrier by special transport systems.⁴

Neurotransmitter synthesis may also be affected by the profile of plasma amino acids. In feeding studies with rats, a high-carbohydrate meal triggered the secretion of insulin, which lowered the blood levels of other large neutral amino acids relative to tryptophan, allowing more trytophan to cross the blood brain barrier and result in increased brain serotonin synthesis.⁵ A high-protein meal had the opposite effect.⁶ Thus, for serotonin, physiologic changes in brain substrate (i.e., tryptophan) levels influence the synthesis of this neurotrasmitter. Whether other neurotransmitters are affected by the profile of plasma amino acids is not known conclusively at the present time.¹

II. Effects of Foods and Nutrient on Behavior

Existing knowledge indicates there is an effect of foods and nutrients on several specific behaviors.

Sleep. According to Dr. Ernest Hartmann with the Tufts University School of Medicine, the administration of tryptophan at levels of 450-600 mg/kg to rats reduced sleep latency (time to sleep). In humans, tryptophan administration to normal subjects or persons with medical or psychiatric problems or with severe insomnia produced inconsistent results; persons with mild insomia, however, generally showed a positive response to tryptophan administration.⁷

In his stuty of sleep behavior in 20 healthy, full-term infants, Dr. Michael Yogman, Harvard Medical School, reported that infants fed a modified formula containing trytophan entered quiet and active sleep phases sooner than they did after being fed a commercial infant formula.⁸

The limited research available indicates that when administered in therapeutic doses, tryptophan may affect sleep patterns in some individuals. It is not known whethher human sleep patterns are affected by tryptophan as a normal constituent of a typical meal.

Alertness and Performance. Dr. Bonnie Spring, Texas Technical University, has studied the effects of carbohydrate (CHO) and protein (PRO) "meals" (actually single food items) on alertness and performance. Subjects were given either a high-PRO meal (trimmed turkey breast) or a high-CHO meal (sherbet). The subjects, particularly females, felt less alert after the CHO than the PRO meal. Older subjects who ate the high-CHO meal for lunch showed impaired concentration on a test of sustained selective attention compared to those who ate the high-PRO meal.9

The effects of meal size and composition on post-lunch performance were reviewed by Dr. Angus Craig of the University of Sussex, England. Dr. Craig reported that the reduction in mental efficiency after lunch appeared to

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be greatest when a heavy, 3-course meal of about 1,000 kilocalories was consumed. This was particularly true if the subject wasn't used to a large meal at lunch. Small, balanced mid-day meals appeared to favor optimun performance and mental efficiency. Meal composition and size may affect mental alertness and performance.

Hyperactivity. One of the first reports of a relationship between the consumption of sugar products and hyperactivity was published in 1980 by Dr. Ronald Prinz of the University of South Carolina. At the symposium, Prinz presented the results of a later preliminary study of 91 nonhyperactive boys aged $4^{1}/_{2}$ to $5^{1}/_{2}$ years. Based on an analysis of 7-day food records, the boys were divided into high-sucrose and low-sucrose intake groups and were given a behavorial test designed to measure attentional performance. Dr. Prinz reported that the boys with a high-sucrose intake scored lower, indicating a poorer attentional performance than boys with a low-sucrose intake.

The results of several sucrose challenge studies were also presented. Dr. Bruce Ferguson at Carleton University studied 8 children who described by their parents as being "sugar responders." The children were given sucrose and aspartame at low, medium and high "doses" and then assessed on a variety of cognitive and behavioral tests. Dr. Ferguson reported that sucrose and aspartame had no effect on behavior or cognitive performance.

Dr. Judith Rapoport with the National Institutes of Mental Health also studied children who were described as "sugar responders" by their parents. Following the administration of glucose, sucrose, and placebo (saccharin) challenges, 21 children were given a 5-hour behavioral tolerance test. Dr. Rapoport reported that the children were less active following the sugar than the saccharin challenges. In a study of 38 hyperactive children given sucrose, fructose and aspartame in an orange drink, Dr. Keith Conners at the National Medical Center reported that sucrose and fructose decreased activity levels. Aspartame had no effect on activity levels.

Hence, results of the challenge studies suggest that sucrose ingestion does not aggravate hyperactivity or contribute to learning or behavioral problems in children. The data cited on alertness suggests sugar ingestion actually makes children sleepy.

Criminal Behavior. Within the correctional community, the belief that violent, aggressive behavior can be controlled by diet is gaining acceptance. The major hypotheses proposed for a diet-criminal behavior link include hypoglycemia, cerebral allergies and addictions, vitamin and mineral deficiencies, environmental contaminants and neurotransmitter imbalances. 11, 12 Few reliable tests of these hypotheses have been published.

Dr. Matti Virkkunen with the Helsinki University Central Hospital, Finland, has studied the response of habitually violent offenders and psychiatric personnel to the 5-hour oral glucose tolerance test (OGTT). He reported that the violent offenders had a more severe and longer lasting hypoglycemic respose to the OGTT than the psychiatric personnel did.¹³, ¹⁴

These studies have been criticized because the criteria for defining hypoglycemia were not clearly established,

violent symptoms were not reported during the OGTT at the time of the glucose nadir; and the offenders were usually long-term alcohol users, a fact expected to influence the OGTT outcome.

There is no evidence that diet causes criminal behavior. Most studies to date in this are have been seriously flawed.¹⁵ Dr. Simon Young at McGill University speculated that persons predisposed to impulsive aggression may be affected by tryptophan administered at therapeutic levels but cautioned that it is not known yet how aggressive behavior may be influenced by diet.¹

III. Strategies for Improving Research

Several strategies for improving research in the diet and behavior area were presented at the symposium:

- 1. Adopt an interdisciplinary approach. Because both variables (diet and behavior) are exceedingly complex, it is necessary to employ a multidisciplinary team in the development, design and implementation of research in this area. Experts from such disciplines as nutrition, biochemistry, psychology, psychiatry, biostatistics, endocrinology, epidemiology, and/or other fields will need to be actively in involved in all phases of diet and behavior research.
- 2. Evaluate nutritional controls in both animal and human studies. To ensure appropriate nutritional control in diet and behavior studies, several issues should be carefully evaluated, including the nutritional adequacy of the diet; the nutritional, physiological and metabolic consequences of dietary modifications; the appropriateness of feeding procedures; the selection of appropriate control groups; the significance of individual variability in response to diet; and the implications of treatments that have adverse effects on health or physical well-being.
- 3. Evaluate and standardize methods for measuring behavioral resposes. It is essential that the method or task used in measuring behavioral changes be capable of detecting effects of diet or nutrients on behavior and provide an accurate and reproducible measurement of the behavioral response. A standardized task should provide reliability, stability, validity and accessibility.
- 4. Improve study designs. Studies of the effects of diet on behavior should involve a multidisciplinary approach. Study protocols should reflect the appropriate use of sampling techniques, control groups, statistics, doubleblind procedures, placebo, minimizing variables, and standardized evaluations. Careful interpretation of research findings is essential.

Conclusion

In summarizing the papers presented at the Diet and Behavior Symposium, Dr. Peter B. Dews of Harward Medical School indicated there was general agreement that diet does appear to affect behavior, but the effects are subtle. For this reason, significant effects of diet on seriously aberrant behavior, such as criminal behavior or hyperactivity in children, would not be expected. Dr.

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Dews commented that "because the field of dietary pharmacology is still in the experimental stage, it is too early to make regulatory decisions or policy changes."

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Resumenes de La Literatura Medica

ACCURACY OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE. Gutgesell HP, Huhta JC, Latson LA, et al. Am J Cardiol 1985; 55:514-518

La ecocardiografía bidimensional (2-D) ha venido a ser la técnica diagnóstica no-invasiva más frecuentemente utilizada en la evaluación de niños con cardiopatías congénitas. Para determinar la especificidad y sensitividad de la ecocardiografía 2-D en el diagnóstico anatómico de las cardiopatías congénitas, la Sección de Cardiología Pediátrica del Hospital de Niños de Texas y de la Universidad de Baylor realizaron este estudio en 126 niños que luego serían sometidos a cateterismo cardíaco.

Las lesiones más frecuentes y la sensitividad y especificidad del ecocardiograma 2-D fueron las siguientes: ducto arterioso patente, 41 pacientes (83% y 100% respectivamente), comunicación interventricular, 35 pacientes (86% y 100%), comunicación interatrial, 26 pacientes (85% y 99%), estenosis pulmonar valvular, 25 pacientes (77% y 97%), transposición de los grandes vasos, 16 pacientes (100% y 100%) y retorno venoso anómalo total, 14 pacientes (85% y 100%). Otros defectos menos comunes diagnosticados por esta técnica fueron: coartación de la aorta (10 de 12), A-V canal (10 de 10), tetralogía de Fallot (10 de 10) estenosis aortica valvular (8 de 8) e interrupción del arco aórtico (4 de 4).

El estudio indica que gran parte de las cardiopatías congénitas puede diagnosticarse por ecocardiografia 2-D y que ecocardiogramas técnicamente satisfactorios pueden obtenerse en la mayoría de los pacientes pediátricos. La información obtenida del presente estudio ayuda a determinar qué cardiopatías pueden diagnosticarse o excluirse por medio de la ecocardiografía 2-D y cuales requiren confirmación por Doppler o cateterismo cardíaco. La estenosis pulmonar valvular y el ducto arterioso patente resultaron ser los defectos donde hubo una mayor incidencia de diagnóstico incorrecto utilizando solamente el ecocardiograma 2-D.

Finalizan los autores enfatizando que aunque el ecocardiograma 2-D puede precisar la anatomía cardíaca en un gran número de pacientes no elimina la necesidad del cateterismo cardíaco y la angiocardiografía. Sobretodo en determinar los variantes fisiológicas y el detalle anatómico de las cardiopatías congénitas complejas.

Rafael Villavicencio, MD, FACC

TUBERCULOSIS: WHEN NOT TO ORDER ROENTGENOGRAMS. Lordi GM, Reichman LB. JAMA 1985; 253:1780-1781

Durante las décadas del 1940 y 1950 cobró auge la detección de la tuberculosis mediante las encuentas radiográficas en masa y los reglamentos haciendo la radiografía de torax obligatoria para entrar en diversas ocupaciones. Esta práctica quedó tan arraigada que, a pesar de lo costosa en relación con el mínimo rendimiento, la misma no ha sido abolida en numerosos departamentos de salud, agencias, etcétera.

La eficacia de los tratamientos preventivos y curativos de la tuberculosis es tanalta que la máxima prioridad se le debe adjudicar a la utilización de la prueba de la tuberculina para detectar las personas en riesgo de desarrollar tuberculosis y a la instauración y supervisión de los programas de tratamiento y prevención de la enfermedad.

Un grupo asesor de la "Food and Drug Administration" ha vertido recomendaciones espécificas sobre las radiografías de torax en tuberculosis las cuales recogen y reflejan los resultados y conclusiones de numerosos estudios, además del sentir de importantes cuerpos como "Centers for Disease Control" y "American Thoracic Society". En síntesis el grupo concluyó que: 1) el rendimiento en términos de casos nuevos descubiertos es insuficiente para justificar el costo de dinero y radiación de radiografías para la búsqueda de casos o repetidas rutinariamente, 2) las radiografías obligatorias como requisito para los empleados son improductivas, 3) las radiografías repetidas en las personas con reacciones significativas (positivas) a la prueba de la tuberculina, con o sin tratamiento con isoniacida, son inútiles, 4) carecen de valor clínico las radiografías de rutina repetidas durante y después del tratamiento antituberculoso.

José E. Sifontes, MD, FAAP

SURVIVAL IN CHRONIC HEPATITIS B-AN ANALYSIS OF 379 PATIENTS. Waisoberg J, et al. Ann Intern Med 1984; 101:613-616

La infección crónica con el virus de hepatitis B afecta actualmente a 175 millones de personas en el mundo. Sin embargo hay gran ignorancia sobre la historia natural de esta enfermedad. Este grupo de investigadores de Stanford (California) analizaron las estadísticas de 379 pacientes con infección crónica por hepatitis B referidos a su institución para tratamiento durante un período de ocho años. A todos los pacientes se les hizo biopsia percutanea de hígado, análisis para HBsAg y determinación de "Hepatitis B DNA polymerase".

De los 379 casos evaluados 121 tenían hepatitis crónica persistente, 128 tenían hepatitis crónica activa y 130 sufrian de hepatitis crónica activa con cirrosis. Cincuenta y un porciento han muerto hasta el comienzo de este análisis. La sobrevida estimada a 5 años desde el momento de contagio fue: 97% para los pacientes de hepatitis crónica persistente, 86% para aquellos con hepatitis crónica activa y 55% para aquellos de hepatitis crónica con cirrosis.

Es interesante señalar el bajo número de mujeres en este grupo de pacientes y que de las presentes muy pocas desarrollaron problemas serios.

Los factores mayormente asociados a un pronóstico pobre fueron: edad sobre 40 años, bili rubina total de más de 1.5 mg/dL, ascitis, y la presencia de arañas vasculares.

Finalmente al compararse con otras series de casos reportados, el pronóstico de los pacientes con hepatitis B crónica activa es similar al de pacientes de hepatitis crónica activa de otras etiologías.

José A. Lozada Román, MD, FACP

RISK OF NOSOCOMIAL INFECTION WITH HUMAN T-CELL LYMPHOTROPIC VIRUS III (HTLV-III). Hirsch MA, Gallo RC, et al. N Engl J Med 1985; 312:1-4

En este estudio el Dr. Robert Gallo y sus asociados analizan el riesgo de infección nosocomial con el virus HTLV-III. Este virus se ha asociado íntimamente con el síndrome de inmunodeficiencia adquirida (SIDA/AIDS). Por tanto existe una gran preocupación en el personal médico y paramédico que entra en contacto con pacientes de AIDS o con muestras tomadas a estos, de contaminarse con el virus arriba mencionado. Los investigadores analizaron para anticuerpos contra el virus HTLV-III la sangre de 85 médicos o técnicos que habían sido expuestos seriamente a sangre o secreciones de pacientes de AIDS. Esta población incluyó 33 casos de punción accidental en la piel con agujas contaminadas.

Todos los sujetos estudiados estaban libres de anti cuerpos contra el virus HTLV-III. Es de interés notar que los 33 técnicos cuya piel fue rota por agujas contaminadas se mantuvieron negativos para el virus, mientras que los 11 pacientes de AIDS que fueron la fuente de contagio mostraron pruebas positivas para el virus.

Concluyen los autores que a pesar de ser este un estudio preliminar, sugiere que el riego de contaminación

con el virus HTLV-III es bajo para el personal médico y paramédico que utiliza las medidas corrientes de aislamiento para sangre y secreciones.

José A. Lozada Román, MD, FACP

LA EVALUACION POR ULTRASONIDO DE INFANTES Y NIÑOS CON INFECCION DEL TRACTO URINARIO. Kangarloo, Hooshang Radiology 1985; 154:367

En este excelente artículo proveniente de los departamentos de Radiología y Pediatría de la Escuela de Medicina de la Universidad de California en Los Angeles, los autores nos relatan su experiencia con 59 pacientes pediátricos con infección del tracto urinario que fueron sometidos a sonografía renal, urografía endovenosa, y cistouretrografía. Las tres modalidades diagnósticas fueron analizadas retrospectivamente para determinar su efectividad relativa en detectar anormalidades que podrían predisponer a estos pacientes a enfermedades infecciosa de las vías urinarias. La cistouretrografía incluyendo vistas durante vaciamiento, proveyó información valiosa, particularmente la presencia o ausencia de reflujo vesicoureteral que no podría haberse detectado con las otras modalidades. La urografía endovenosa fue menos específica que el ultrasonido en la mayoría de los pacientes, con la excepción de aquellos que tenían cambios cicatriciales renales. Los autores recomiendan la sonografía como la modalidad inicial de evaluación de elección en estos niños con enfermedad infecciosa de las vías urinarias. Cuando el sonograma es normal, la urografía endovenosa no se considera necesaria pero el cistouretrograma con placas de vaciamiento es esencial. Si el sonograma renal es anormal, la urografía endovenosa y/u otros estudios diagnósticos están indicados.

Bernardo Marqués, MD

COLON POLYPS AND CARCINOMAS: PROSPECTIVE COMPARISON OF THE SINGLE AND DOUBLE-CONTRAST EXAMINATION IN THE SAME PATIENTS. De Roos A, Radiology 1985; 154:11

Single-contrast (SC) and double-contrast (DC) colon examination were compared in 425 consecutive patients for detection of polyps and stricturing carcionomas. Each patient was examined with both SC and DC during the same session. In patients with carcinoma, there was no significant difference between the two modalities. DC was far superior to SC for detection of rectal or colonic polyps; however, the techniques appeared to be complementary in the sigmoid and cecum. The author concludes that DC is superior to SC as a mean of screening for polyps to the rectum and colon, with SC being useful as an adjunct in problem areas such as the sigmoid and cecum.

Bernardo Marqués, MD



What can you do for hypertensives like Laura K?



Frequently misses one or more of her three daily pills.

Lives alone

Doesn't cook much "from scratch." Eats mostly processed foods.

Worsening

Controlled at last visit but now her diastolic reads 101 mmHg... age 64.

Depressed

Sleeps badly and sometimes has bad dreams.

0 0 1 00 0

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Laura K represents 5,335 women between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Few CNS effects

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN—making it an excellent choice for patients like Laura K, who may experience CNS effects with other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Laura K...and virtually all your hypertensive patients

TENORMIN® (atendal)





and virtually all your hypertensive patients

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) DESCRIPTION: TENORMIN' (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2²-hydroxy-3²-[41-methylethyl) amino] propoxy]. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25° C) and less soluble in chlorotorm (3 mg/ml at 25° C) and less soluble in Chipman (3 mg/ml at 25° C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiszyde-type dureter.

thiazide-type durete

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia. heart block greater
than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory
function in congestive heart failure, and beta blockade carries the potential hazard of further
depressing myocardial contractility and precipitating more severe failure. In hypertensive patients
who have congestive heart failure controlled by digitals and diuretics. TENORMIN should be
administered cautiously. Both digitalis and atenolos lsow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with
heta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. It cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn. Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial inflarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectors, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it with-drawal symptoms occur.

drawal symptoms occur
Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initilated
at 50 mg and a beta,-stimulating agent (bronchodilator) made available. If dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood
levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN betore surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg. profound bradycardia hypotension) may be corrected with atropine (1-2 mg I V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask fachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. fachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyriod storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with

Should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION)

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis. Mutagenesis. Impairment of Fertility: Two long-term (maximum dosing dura-

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study each employing dose levels as high as 300 mg / kg / day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding

Fertility of male or temale rats (evaluated at dose levels as high as 200 mg / kg / day or 100 times the maximum recommended human dose) was unaffected by atenolol administration. **Animal Toxicology:** Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and temale dogs at all tested dose levels of atenolol (starting at 15 mg /kg /day or 7 5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol / kg / day (150 and 75 times the maximum recommended human dose, respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo / tetal resorptions in rats at doese equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12 5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justilies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol

APPENDED TO BE SAIETY AND EFFECTION AND TEMPORARIES TO BE SAIETY AND EFFECTION AND TEMPORARIES is similar, causal relationship is uncertain

Is stiffular, causar relationality is uncertaint. The following adverse-reaction data present frequency estimates in terms of percentages, first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered).

trom the U.S. studies (volunteered side effects) and then trom both U.S. and foreign studies (volunteered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%),

CENTRAL NERVOUS SYSTEM./NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headeness (1%-0.9%), liredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0.9%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), dreaming (0%-0.9%)

GASTROINTESTINAL diarrhea (2%-0.9%), nausea (4%-1%), dyspnea (0.6%-1.9%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR bradvazrdia (3%-0.9%), cold extremities (12%-5.9%), postural hypotension

TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), latigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS), wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored tollowing cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenoloi)

TENORMIN (atenoiol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatoria, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-

place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics Gastrointestinal; Mesenteric arterial thrombosis, ischemic colitis Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOS AGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart tailure, hypotension,

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart tailure, hypotension bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or noreproperhine may be useful in addition to atropine and digitals.

nephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine

Hypoglycemia: Intravenous glucose
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any turther benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including.

TENORMINI may be used alone or concomitating with other artimypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance talls below 35 m1/min. 1.73 m² (normal range is 100-150 m1/min.1.73 m²), therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml min 173 m²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
< 15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

References: 1. Data on tile, Stuart Pharmaceuticals 2. Herman RL, Lamdin E, Fischetti JL, Ko HK Postmarketing evaluation of atenolol (Tenormin*) A new cardioselective beta-blocker *Curr Ther Res* 1983. 33(1) 165-171 3. Zacharias FJ Comparison of the side effects of different beta blockers in the treatment of hypertension *Primary Cardiol* 1980, 6(suppl 1) 86-89



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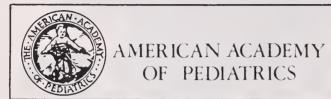


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CHILDREN, ADOLESCENTS, AND TELEVISION

Next to the family, television may be the most important source of information for children and a principal factor influencing their development. Children two to 12 years old in the United States watch approximately 25 hours of television per week. On an annual basis, children spend more time in front of their television sets than they spend in school.

Television is a powerful tool that can promote learning, create aspiration, and induce prosocial behavior. When it deals with medical topics, television contains many messages that promote health or prevent illnes. However, television advertising and programming can adversely affect learning and behavior of children and adolescents in a number of significant areas:

- 1. Repeated exposure to televised violence promotes a proclivity to violence and a passive response to its practice.
- 2. Television viewing increases consumption of high caloric density snacks, and increases the prevalance of obesity.
- 3. Although the evidence that television may have a deleterious effect on school performance may be confounded by other factors, learning from television is passive rather than active, and detracts from time spent reading or using active learning skills.
- 4. Television conveys unrealistic messages regarding drugs, alcohol, and tobacco, and indirectly encourages their use.
- 5. The portrayal of sex roles and sexuality on television is unrealistic and misleading: sexual relationships develop rapidly; the risk of pregnancy is rarely considered; adolescence is portrayed as a constant state of sexual crisis. These characteristics may contribute directly or indirectly to the risk of adolescent pregnancy and clearly alter age-dependent experiential learning with respect to sexuality. Pornography on cable television is a particularly important concern.
 - 6. Television promotes ethnic and racial stereotypes

and does little to promote a sympathetic understanding of handicapped people.

7. Television conveys an unrealistic view of problem solving or conflict resolution.

To address these concerns, we recommend that the American Academy of Pediatrics:

- 1. Educate pediatricians with respect to the consequences of television viewing. Approaches should include the development of specific materials and curricula for teaching medical students, pediatric house staff, practing pediatricians, and others who deal directly with the health of children and adolescents.
- 2. Provide materials and an approach to counseling children, adolescents and their families regarding the effects of television and methods suitable for altering viewing habits. Although an AAP pamphlet already existis for this purpose, additional materials regarding alcohol and sexuality would be useful. Specific recommendations for counseling should be developed.

3. Encourage legislative activity to increase quality programming and reduce advertising directed at children.

- 4. Establish liaisons with networks, producers, writers, and other professional organizations to improve the quality of programming and advertising and to act as a resource for these groups.
- 5. Provide an ongoing review of new technologies that enable families to alter or control their children's television viewing habits.
- 6. Encourage involvement by local and chapter groups to interact with network affiliates, independent television stations, and cable companies to improve local programming and advertising directed at children.

Task Force on Children and Television H. James Holroyd, M.D., Chairman S. Norman Sherry, M.D. Frank Palumbo, M.D. Victor Strasburger, M.D. William H. Dietz, Jr., M.D., Ph.D.

SMOKING AROUND CHILDREN INCREASES THEIR CHANCE OF RESPIRATORY PROBLEMS

When parents worry about the health of children, it should include more than just shots, accidents and behavior.

Passive smoking—the inhalation of cigarette smoke by infants and children— has acute health effects, reported a medical expert at the American Academy of Pediatrics (AAP) Spring Meeting last April.

"Children who live with parents who smoke have an increased incidence for health problems," said Michael Wall, M.D., an Associate Professor of Pediatrics and director of the Oregon Health Sciences University Pediatric Pulmonary Disease Section.

One problem includes an increase in lower respiratory tract infections in children under one year of age. "Some of these children can get quite severely ill," Dr. Wall reported.

Another association linking passive smoking to poor health includes a household with a smoker and a child with an existing lung disease or condition such as asthma, the Portland pediatrician said.

"It compounds the problem. The exposure to smoke can make the child's condition acutely worse."

Though the long-term effects of passive smoking have not been fully documented, Dr. Wall mentioned most studies in older children have shown that children who live with smokers have a lower lung function during testing than those in a "non-smoking" environment.

"Whether or not lower levels of lung function can lead to significant health problems later in life is not yet known, so we do have to be cautious in this research aspect of passive smoking's effect on children," Dr. Wall said.

Nevertheless, Dr. Wall told the nation's pediatricians to read the medical literature on the proven health effects of passive smoking and to make these known to parents.

"But, be careful not to imbue parents with such guilt that they storm out or your office. Try to be sensitive and offer alternatives to them," Dr. Wall concluded.

BETTER NEONATAL TECHNIQUES SAVING LOW-BIRTHWEIGHT INFANTS

Twenty years ago, babies born less than 1000 grams (2 pounds, 3 onces) had a mortality rate of more than 90 percent and a high incidence of handicaps.

Today, however, through better medical techniques, extremely low-birthweight children born in the U.S. and in developed countries have a better chance of survival and escaping handicaps.

Most importantly, though, is that infants born between 500-1000 grams have a better than 50/50 chance of appearing normal at 1 to 2 years of age if they survive, said Ernest Kraybill, M.D., who spoke today at the American Academy of Pediatrics (AAP) Spring Meeting.

Dr. Kraybill, a professor of pediatrics at the University of North Carolina, reported that extremely low-birthweight infants, even those who appear normal at 1 to 2 years of age, are at a high-risk for learning disabilities and require close pediatrics services.

Yet, in reporting statistics about mortality and handicap rates for these types of infants, Dr. Kraybill noted that prompt resuscitation, prevention of hypoxia, prevention of chilling, good nutrition and especially assited ventilation have allowed neonatologists the chance to save these infants.

"To illustrate the outcome of infants born between 500-1000 grams, let's take a look at a couple of recent studies," Dr. Kraybill said.

One population-based study conducted in Australia and two conducted in Canada found mortality rates of 56-75 percent in infants born between 500-1000 grams. Of the survivors, about 50 percent appeared normal at 2 years of age; about 38 percent had mild/moderate handicaps; and approximately 14 percent had severe impairments.

In four U.S. hospital-based studies, Dr. Kraybil noted mortality rates of 55-81 percent in infants born between 500-800 grams (during the first year of life).

"And if you look at the survivors in these particular studies, you'll find that about 60 percent appeared normal at 1 to 2 years of age; 20-25 percent had mild/moderate handicaps; and nearly 15 percent had severe handicaps," he said.

In summary, Dr. Kraybill said that small increments of birthweight can mean a lot where survival is concerned.

"Survival at 700 grams is better than at 600 grams; and survival at 600 is better than 500. In contrast, the risk of handicap among survivors is fairly uniform between birthweights of 500-1000 grams," he said.

SWIMMING POOL SAFETY

Each year, there are between 600 and 650 pool drownings in the United States. Swimming in home pools is associated with higher accident rates that swimming in public pools where supervision is better.

Annual data regarding swimming pool fatalities is available in the "Swimming Pool Accident Report" published annually by Water Safety Services, an aquatic research and safety organization. Their current report indicates that:

- Seventy percent of pool victims are male.
- More than half of the pool fatalities occur in single-family, residential pools.
- Forty-four percent of victims are under eleven years of age and thirty-three percent are under five years of age.
- Three-year-olds are most vulnerable to drowning accidents

Swimming pool drownings and the equally tragic neardrownings are usually the result of poor supervision of children or pools that are inadequately secured when adults are absent.

Pediatricians can encourage responsibility among pool owners both by counseling individual families and by participating in community-wide safety programs.

AAP-Accident Prevention Newsletter

PEDIATRICIANS PRESS FOR IMMEDIATE ASPIRIN LABELING TO WARN OF REYE SYNDROME HAZARDS

In testimony presented before Congress last March, the American Academy of Pediatrics (AAP) questioned the effectiveness of voluntary labeling to warn consumers about the possible association between aspirin use and Reye Syndrome.

A pilot study conducted by the U.S. Public Health Service this year to investigate the link between aspirin and Reye Syndrome revealed that a surprising number of the Syndrome's victims were adolescents who presumbly took adult-strength aspirin without physician advice.

Speaking before the House Subcommittee on Health and the Environment, Albert A. Pruitt, M.D., chairman of the AAP's Committee on Drugs and the chairman of the Department of Pediatrics at the Medical College of Georgia, said, "There is now more reason than ever to warn the public -especially adolescents - about the association between aspirin and Reye Syndrome."

"The study strongly indicates that aspirin can no longer be regarded as an appropriate medication for children or young adulst with flu or with an illness which might be chicken pox," Dr. Pruitt said. "Because aspirin is largely self-medicated by young adults, it is important that the labeling read by the consumer be unabiguous on this point."

Dr. Pruitt pledged the Academy's full support of aspirin labeling which would provide current information about the relationship between aspirin and Reve Syndrome. Last month Representative Henry A. Waxman (D-CA) introduced H.R. 1381, the Emergency Reye's Syndrome Prevention Act, which would mandate aspirin labeling.

Although the specific cause of Reye Syndrome is not known, four previous studies also have linked its development to the use of aspirin in treating children and adolescents with such viral infections as chicken pox or flu. Reye Syndrome is characterized by a brief improvement in the child's condition, followed by severe

vomiting, coma and convulsions. Permanent damage to the nervous system and death can result.

When the results of the USPHS study were reported in February, the nation's major aspirin manufacturers agreed to make label changes and to issue warnings that the drug should not be used to treat children or teenagers with chicken pox or flu. The AAP expressed its disappointment that the message about aspirin and Reye Syndrome is not getting to the consumer and questioned the effectiveness of voluntary labeling.

"We recognize the urgency of definitive action and would hope this hearing will serve as the necessary catalyst to encourage a suitable response by the industry," Dr. Pruitt said. "Ideally, we feel labeling can work without legislation. But as a practical matter, it may not."

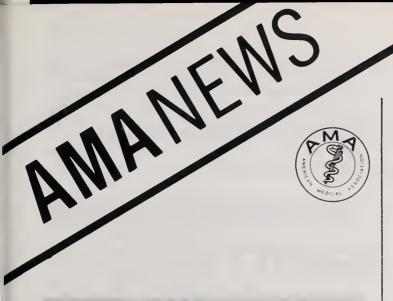
Dr. Pruitt reported that several of the Academy's technical committees will be reviewing the data from the USPHS study, but suggested that further research in this are must be continued. The Public Health Service is considering a more complete follow-up study to the one completed earlier this year.

The AAP testified only on the issue of effective labeling programs and not on the issue of further studies of the possible link between aspirin and Reye Syndrome. "When our children are at risk, they most certainly deserve the benefit of any doubt," Dr. Pruitt said.

You may find it surprising that up to 60% of all cancers can be prevented. By avoiding excessive exposure to sunlight, by not smoking cigarettes, by not overeating and by following a diet high in fiber and low in fat.

The battle isn't over but we are winning. Please support the American Cancer Society. Society.

AMERICAN



COMPUTED TOMOGRAPHY REDUCES DIAGNOSTIC COSTS DRAMATICALLY

Use of computed tomography (CT) can substantially reduce the cost of diagnosing brain injuries, according to a report in an April issue of JAMA.

At the Mayo Clinic in Rochester, Minn., Michael Garraway, MD, and colleagues studied the impact of CT in diagnosing subdural hematoma in one Minnesota county from 1965 through 1980. Sixty cases of subdural hematoma occurred from 1965 to 1972, before CT was available; these cases were compared with 46 cases that occurred after the introduction of CT in 1973.

"The advent of CT did not change the treatment course of the disease or prognosis of subdural hematoma," the researchers say. "However, the introduction of CT had a marked effect on the pattern of neurological investigation carried out. This resulted in a 15 percent reduction in the cost of diagnosing subdural hematoma in this community." The researchers add that the overall cost of health care rose by 87 percent during the same period nationwide.

The researchers say that subdural hematoma provides a useful disease model to evaluate the impact of CT because diagnosis is often difficult, especially among the elderly. They add that early diagnosis and prompt treatment greatly enhance recovery. The main effect of introducing CT was a reduction in other diagnostic procedures, including angiograms, echoencephalograms and electrocephalograms. The study showed that more than 60 percent of the patients before 1972 had an angiography, whereas only 17 percent had the procedure after 1977.

The researchers add that although their study did not assess false-positive results of CT in diagnosing subdural hematoma, only two CT scans were normal in patients later found to have the condition (false negatives). They say other studies have shown the accuracy of CT in detecting intracranial hematoma approaches 100 percent. An earlier study at the Mayo Clinic suggested that diagnostic errors occur in fewer than 10 percent of patients and are equally divided between false-positive and false-negatives.

"The introduction of new medical technology is under

almost continuous attack because of the implications of an increase in health care costs," the researchers say. They conclude that more studies on the use of CT will be helpful in determining whether this procedure reduces costs in diagnosing other neurological disease as well.

JAMA April 26, 1985

TRAVELERS' DIARRHEA CAN BE PREVENTED, TREATED: NIH

Diarrhea is by far the most common health problem of travelers to developing countries, but there are ways to prevent or treat it, according to a Consensus Conference report from the National Institutes of Health published in JAMA.

The report says diarrhea may occur in as many as 20 to 50 percent of travelers to high risk areas in Latin America, Africa, the Middle East and Asia. The syndrome is caused by infection resulting from ingestion of fecally contaminated food or beverages; Escherichia coli is the most common cause of travelers' diarrhea in all countries where surveys have been conducted.

"Prudent dietary and hygenic practices should be followed, and they will prevent some, but not all, diarrhea," the report says. High risk foods include raw vegetables, raw meat and raw seafood, but tap water, ice, unpasteurized milk and other dairy products and unpeeled fruits have also been implicated. Food from street vendors carries the highest risk. The report adds that bottled carbonated beverages, beer, wine, hot coffee or tea, or water that has been boiled of treated with chlorine or iodione are all safe. If diarrhea occurs despite dietary caution, the report recommends antimotility drugs such as diphenoxylate (Lomotil) or loperamide, or bismuth subsalicylate (Pepto-Bismol), which works more slowly. For severe cases, antimicrobial drugs such as trimethoprim-sulfamethoxazole, trimethoprim alone or doxycycline are recommended. The report cautions against using any of these drugs prophylactically; the first drugs may make symptoms worse, and the antimicrobials can have serious side effects. Purchasing the drugs before the trip is advised. Increased fluid intake is also recommended.

JAMA May 10, 1985

BREAST FEEDING MAY SAVE INFANTS WITH PROTEIN DEFICIENCY

Breast feeding may offer some protection against severe liver disease and death in infants with alpha₁-antitrypsin deficiency, according to a report in JAMA. Deficiency of the protein increases the risk of liver disease and dysfunction that can be fatal.

John N. Udall, Jr., MD, PhD, of Massachusetts

General Hospital, Boston, and colleagues studied the influence of early feeding practices on subsequent development of liver disease in 32 children with a₁-antitrypsin deficiency. Twelve of the children had been breast fed during the first month of life and 20 had been bottle fed. The groups were similar in birth weight, age an serum a_1 -antitrypsin concentration.

"Only one of the 12 breast-fed developed severe liver disease," the researchers say. "None of the eight infants who were breast fed for two months or longer developed severe liver disease." In contrast, eight of the 20 bottlefed infants developed severe liver disease and seven died.

The researchers note that human milk contains enzyme inhibitors, including a_1 -antitrypsin, and suggest that the more alkaline pH of an infant's stomach permits these inhibitors to reach the small intestine, where they can neutralize certain enzymes. They say breast feeding is known to protect against other diseases, including atopic dermatitis, bacterial and viral infections, acrodermatitis enteropathica, congenital hypothyroidism and inflammatory bowel disease.

The researchers say that liver disease associated with a₁-deficiency occurs most often in infants and also occurs more frequently in males. Eighty percent of the children in their study were males.

The study may have had some bias because women of a higher socioeconomic status are more likely to breast feed their infants and to have access to better health care. The researchers also suggest that other factors in breast milk and other environmental factors may have influenced the infants' health. They conclude, however, that since this study showed a significantly higher mortality rate among bottle-fed infants with a₁-antitrypsin deficiency, further investigation is needed to clarify the factors involved.

JAMA May 10, 1985

IBUPROFEN RELIEVES SOME ULTRAVIOLET SYMPTOMS

Ibuprofen was more effective than placebo for relief of symptoms associated with inflammation after high dose ultraviolet-B phototherapy for treatment of psoriasis in a double-blind study of 19 patients, according to a report in the April Archives of Dermatology. Robert S. Stern, MD, and Thomas B. Dodson of Beth Israel Hospital in Boston say the phototherapy is helpful for psoriasis, but often is accompanied by inflammation and sometimes by pain, development of vesicles, fever and chills. They say ibuprofen helps relieve inflammation, "but the drug has limited usefulness in the treatment of sunburn reaction from these same does (in phototherapy)."

CITE BETTER CONTROL FOR HEAD AND NECK CANCER

Preoperative use of mitomycin and fluorouracil and concomitant radiotherapy offer encouraging results in the control of head and neck cancer, according to a report from the Virginia Medical Center in Charlottesville.

Michael J. Kaplan, MD, and colleagues say they treated 42 patients with stage IV squamous cell carcinoma (the most critical stage of the disease). For the entire group, 27 had a complete response to treatment, 14 had a partial response, and 1 had no response. "Follow-up is between 10 months," the researchers say in the April Archives of Otolaryngology. Kaplan now is at the University of California, San Francisco.

DELTA AGENT MAY KILL HEPATITIS VICTIMS

Fatal complications can occur in asymptomatic hepatitis B virus carriers following delta agent infection, according to a report in the May Archives of Pathology and Laboratory Medicine. Sugantha Govindarajan, MD, and colleagues report on the case of a 36-year-old homosexual man who had been a hepatitis B carrier since 1972 and who was infected by the delta agent in 1982. The delta agent is a defective RNA virus, requiring the helper function of hepatitis B virus for initiation and replication in the liver. The patient reported on died 15 months after delta agent infection, due to bleeding esophageal varices and advanced cirrhosis, according to the pathologists from the Rancho Los Amigos Hospital in Downey, Calif.

CHILDHOOD POISONINGS SIGNAL OF FAMILY DISTRESS

Serious ingestions of poisons in preschool children appear linked to family distress, especially maternal distress, according to a study from Harward Medical School in Boston. William G. Bithoney, MD, and colleagues measured families in 23 hospitalized children along with controls matched by age, race and socioecomic status. Using six variables as a screening device, the researchers were able to classify correctly 87 percent of the subjects as either case children or controls. Among the variables were lack of extended family, few maternal opportunities to escape care-giving, and a high frequency of physical punishment in the mother's childhood, the researchers say in the May American Journal of Diseases in Children.

ASOCIACION PUERTORRIQUEÑA DEL CORAZON

SESION CIENTIFICA ANUAL CARDIO 85

13, 14, 15 DE SEPTIEMBRE DE 1985 CERROMAR, DORADO RESUMEN DE PONENCIAS (CALL FOR ABSTRACTS)

El Comité del Programa Científico invita a enviar abstractos de trabajos originales para considerarse para presentación durante la sesión científica que se efectuará los días 13, 14, 15 de septiembre de 1985, como parte de la Asamblea Anual de la Asociación Puertorriqueña del Corazón.

Para más información escriba a:

Dr. Salomón Monserrate Presidente, Comité Científico Asociación Puertorriqueña del Corazón Calle Cabo Alverio #554 Hato Rey, Puerto Rico 00918

Fecha límite para entregar los trabajos: 1ro de junio de 1985



CERTAMEN

PATROCINADO POR LA ASOCIACION PUERTORRIQUEÑA DEL CORAZON Y LA SOCIEDAD PUERTORRIQUEÑA DE CARDIOLOGIA.

"PREMIO AL INVESTIGADOR JOVEN DE LA SOCIEDAD PUERTORRIQUEÑA DE CARDIOLOGIA"

PREMIOS: El ganador recibirá un boleto ida y vuelta para asistir a la próxima reunión científica de cardiología (American Heart Association o American College of Cardiology más \$500.00 para gastos de hotel y comida.

ELEGIBILIDAD: Médicos que estén en entrenamiento postgraduado o que no hayan pasado más de 3 años desde que terminó su entrenamiento. Estudiantes de medicina y candidatos a PhD son también elegibles.

OBJETIVOS: Presentar un trabajo de investigación en el campo de la cardiología en CARDIO 85. La presentación será de 12 minutos de duración, describiendo el trabajo original en el cual el autor fue el principal investigador.

PROCEDIMIENTO: 1. Someter un trabajo de investigación (original y 5 copias).

2. Enviar resumen a:

PREMIO AL INVESTIGADOR JOVEN

Asociación Puertorriqueña del Corazón

Cabo Alverio 554

Hato Rey, Puerto Rico 00918

FECHA LIMITE: 30 de mayo de 1985.

FAVOR DE SOLICITAR LAS FORMAS DE PARTICIPACION EN EL CERTAMEN "PREMIO AL INVESTIGADOR JOVEN" EN LA ASOCIACION PUERTORRIQUEÑA DEL CORAZON.

PARA MAYOR INFORMACION FAVOR DE LLAMAR A:

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References: 1. Kales J et al: Clin Pharmacol Ther 12:691-697, Jul-Aug 1971. 2. Kales A et al: Clin Pharmacol Ther 18:356-363. Sep 1975. 3. Kales A et al: Clin Pharmacol Ther 19:576-583, May 1976. 4. Kales A et al: Clin Pharmacol Ther 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: J Am Geriatr Soc 27:541-546, Dec 1979. 6. Kales A, Kales JD: J Clin Pharmacol JTher 21:355-361, Mar 1977. 8. Zimmerman AM: Curr Ther Res 13:18-22, Jan 1971. 9. Amrein R et al: Drugs Exp Clin Res 9(1):85-99, 1983. 10. Monti JM: Methods Find Exp Clin Pharmacol 3:303-326, May 1981. 11. Greenblatt DJ et al: Sleep 5(Suppl 1):S18-S27, 1982. 12. Kales A et al: Pharmacology 26:121-137, 1983.

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instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/ or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

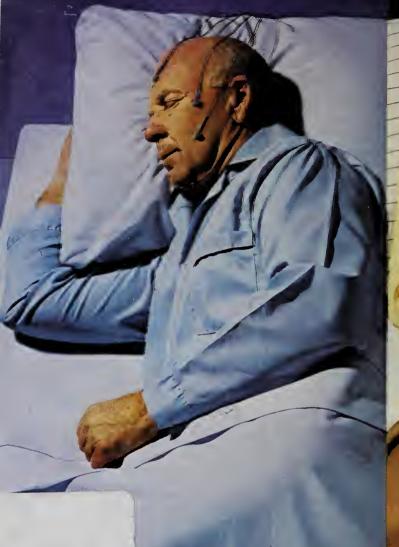
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, fry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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